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THE NORMAL CEREBRAL ANGIOGRAM*

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SINCE Egas Moniz[3] first advocated the use of cerebral angiography for determining the location and nature of intracranial lesions, the method has become increasingly popular. The technique was first used extensively in European clinics; however, the recent appearance of several articles[10,12,14,22] in the American literature indicates that cerebral angiography is rapidly attaining an important position in this country.

An intimate knowledge of the normal cerebrovascular relationships and of the normal anatomical and physiological variations is a prerequisite to the interpretation of cerebral angiograms. In our early experience these variations were a source of great confusion to us and the need for a comprehensive study of them was soon realized. This paper reports on such a study and is based not only on our own series of cases but also on cases reported by others.

Our observations of normal angiographic anatomy were made from the films of 50 patients who had no space-occupying intracranial lesion that could be determined by history, physical examination, and subsequent clinical course. Pneumoencephalography or ventriculography was performed in 66 per cent of these patients and revealed no significant abnormality. The majority of these patients had either idiopathic epilepsy or subarachnoid hemorrhage of undetermined etiology. Admittedly, it would have been desirable to study the cerebral angiograms of entirely normal persons, but we did not feel justified in obtaining these since there is some risk associated with the intravenous injection of any of the available contrast media. This series of 50 patients was selected from a total of 210 patients who had cerebral angiography performed at The Johns Hopkins Hospital over a sixteen month period. Our experience with vertebral angiography is limited to 5 normal cases and our discussion of the variations encountered in vertebral angiography is therefore necessarily brief.

The technique of cerebral angiography has been described in detail by a number of workers.[2,10,12,14,22] In our series of cases, percutaneous puncture of the common or internal carotid artery for carotid angiography, or of the vertebral artery for vertebral angiography, was carried out following infiltration of the skin of the neck with 1 per cent procaine. A series of four injections, each consisting of 15 cc. of 35 per cent diodrast, was rapidly performed, and films designed to show the arterial, capillary and venous phases of the cerebral circulation were obtained. An automatic cassette

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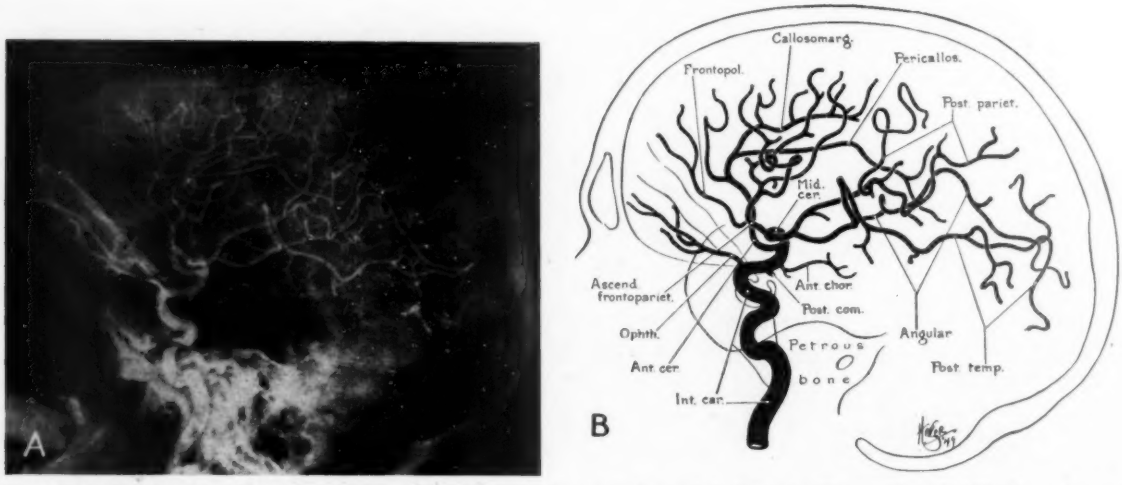

FIG. 1. (*A*). Lateral view of the normal carotid angiogram (arterial filling). (Retouched.) (*B*) Drawing of (*A*). The main cerebral arteries are labelled.

changer is of definite value in timing the initial exposure and controlling the time interval between each subsequent film. In the future we plan to use such a device but have obtained fairly satisfactory results with simpler apparatus.

ANATOMY OF THE CEREBRAL VESSELS

Two pairs of arteries form the blood supply to the intracranial contents: (a) the internal carotid and (b) the vertebral arteries. The internal carotid artery, which is formed by the division of the common carotid artery into the internal and external carotid arteries, enters the skull through the carotid canal and emerges in the medial part of the floor of the middle fossa. From this point the internal carotid artery follows a tortuous course along the side of the sella turcica before it pierces the inner layer of the dura mater and divides into its terminal branches, the anterior and middle cerebral arteries (Fig. 1*A* and *B*, 2*A* and *B*). From the point of bifurcation the anterior and

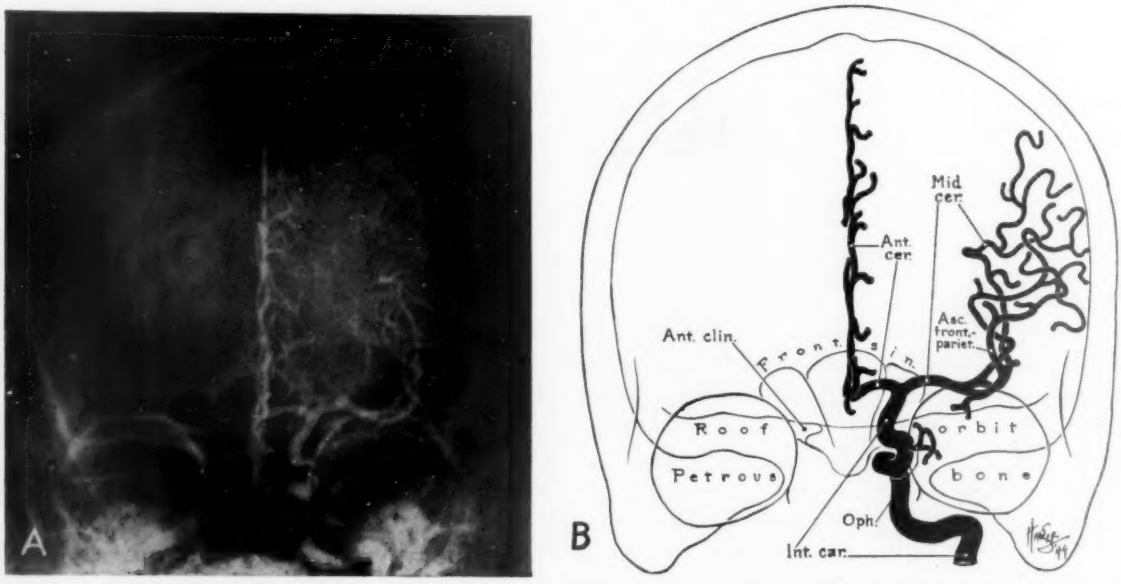

FIG. 2. (*A*) Anteroposterior view of the normal carotid angiogram (arterial filling). (Retouched slightly.) (*B*) Drawing of (*A*). The main cerebral arteries are labelled.

middle cerebral arteries proceed in opposite directions. The anterior cerebral artery courses directly to the midline where it ascends between the cerebral hemispheres and roughly outlines the superior boundary of the corpus callosum. The middle cerebral artery extends laterally deep in the sylvian fissure and then follows the sylvian fissure superiorly and posteriorly for a variable distance before emerging from it to extend over the surface of the brain.

The paired vertebral arteries, one of which arises from the left subclavian artery and the other from the right subclavian artery, enter the skull through the foramen magnum and unite along the lower border of the pons to form the single basilar artery. The basilar artery in turn divides into two divisional branches, each of which continues as the posterior cerebral artery of that side (Fig. 3, 4 and 5).

The carotid system and the basilar system are joined by the posterior communicating arteries to form the circle of Willis. Thus, the circle of Willis is formed by the anterior communicating artery (which is an anastomosis between the two anterior cerebral arteries), the paired proximal portions of the anterior cerebral arteries, the paired supraclinoid portions of the internal carotid arteries, the paired posterior communicating arteries, and the paired divisional branches of the basilar artery. The circle of Willis is schematically shown in Figure 6. In cerebral angiography the entire circle of Willis is never visualized, but only those portions of the circle which are formed by the carotid or basilar system. The connection between the basilar and carotid systems is of practical importance since sometimes one system fills through this anastomosis when the other system is injected with contrast medium.

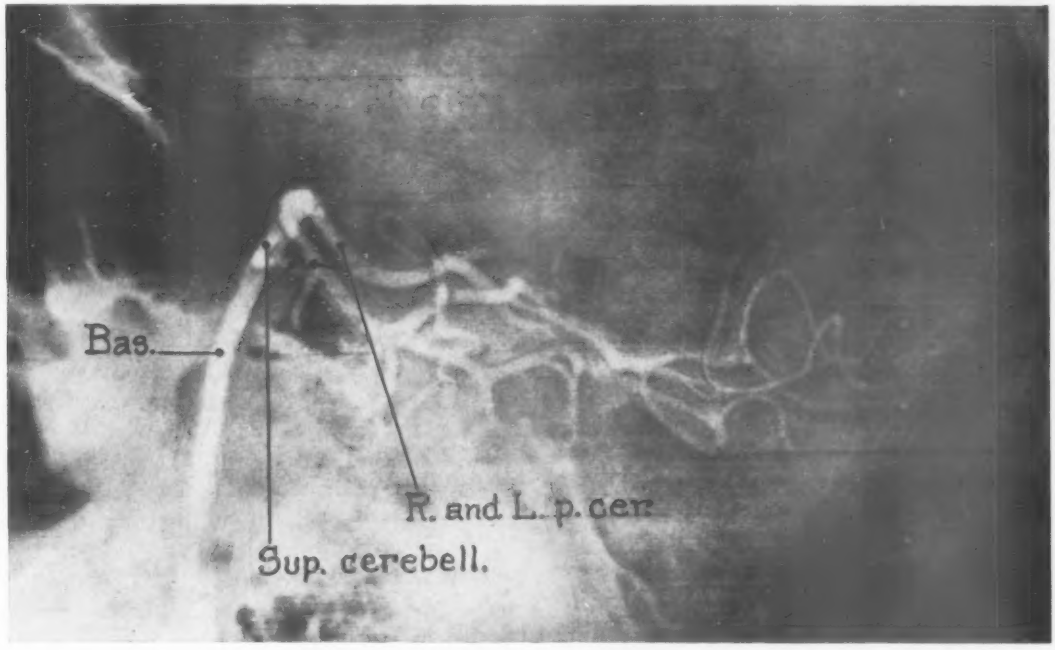

Fig. 3. Lateral view of normal vertebral angiogram (arterial filling). Illustrates filling of both posterior cerebral arteries. (Retouched.)

The capillary system is visualized angiographically as a diffuse opacification of the brain. The individual capillaries are not seen because of their small size.

The venous system may be divided into the superficial cerebral veins, the deep cerebral veins, and the dural sinuses (Fig. 7 *A* and *B*, and 8). The superficial cerebral veins cover the outer surface of the cere-

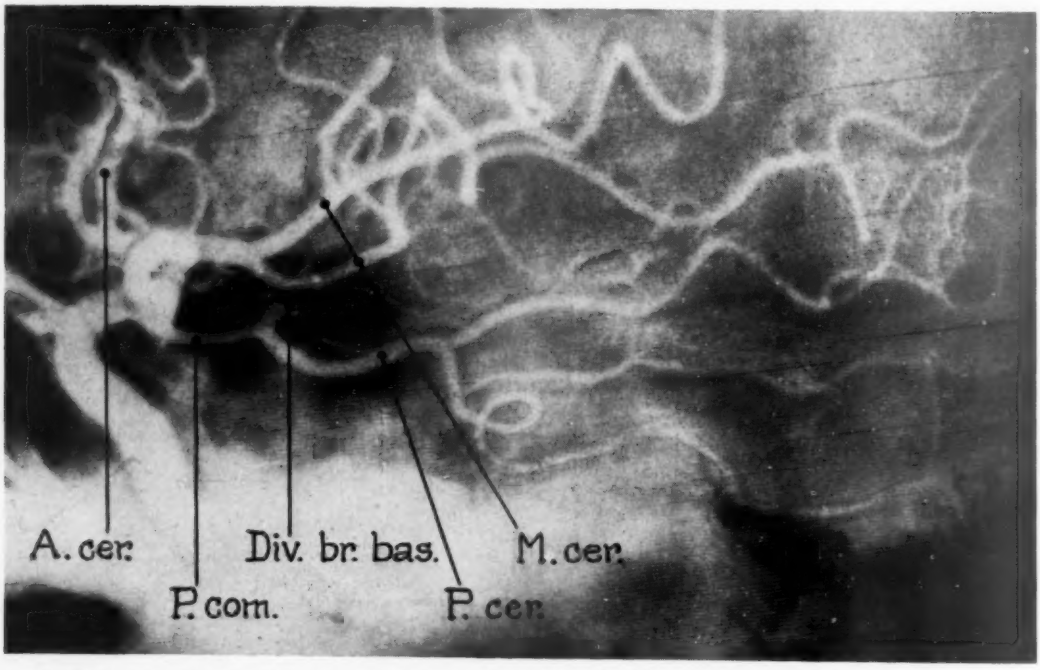

Fig. 4. Lateral view of normal carotid angiogram (arterial filling). There is filling of the ipsilateral posterior communicating artery, posterior cerebral artery and divisional branch of basilar artery. Note characteristic bifurcation of posterior cerebral artery into superior and inferior branches. (Retouched.)

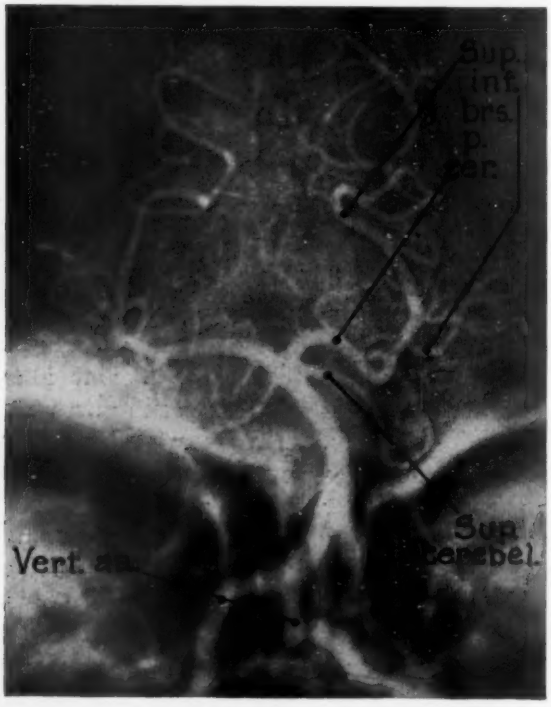

Fig. 5. Anteroposterior view of normal vertebral angiogram (arterial filling). Both vertebral arteries are filled. Observe marked tortuosity of the basilar artery. Superior cerebellar and posterior cerebral arteries are well demonstrated. Notice symmetry in position and configuration of the posterior cerebral arteries. (Retouched.)

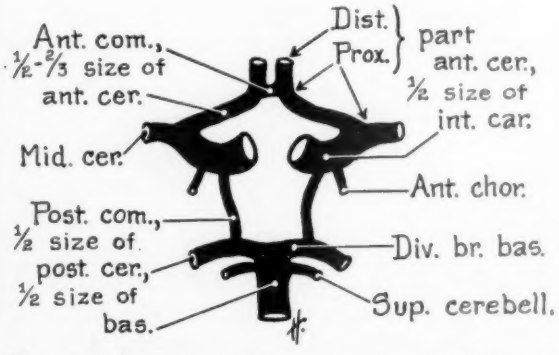
Ant. com., ½-⅔ size of ant. cer.
Dist.
Prox.
part ant. cer., ½ size of int. car.
Mid. cer.
Ant. chor.
Post. com., ½ size of post. cer., ½ size of bas.
Div. br. bas.
Sup. cerebell.

Fig. 6. Schematic drawing of circle of Willis with labelling of its component vessels. Relative sizes of the different arteries are given.

brum and drain into the superior longitudinal and the transverse sinuses. The deep cerebral veins consist of the paired internal cerebral veins and the paired basal veins of Rosenthal which unite to form the great vein of Galen. This latter vessel extends around the splenium of the corpus callosum to empty into the straight sinus

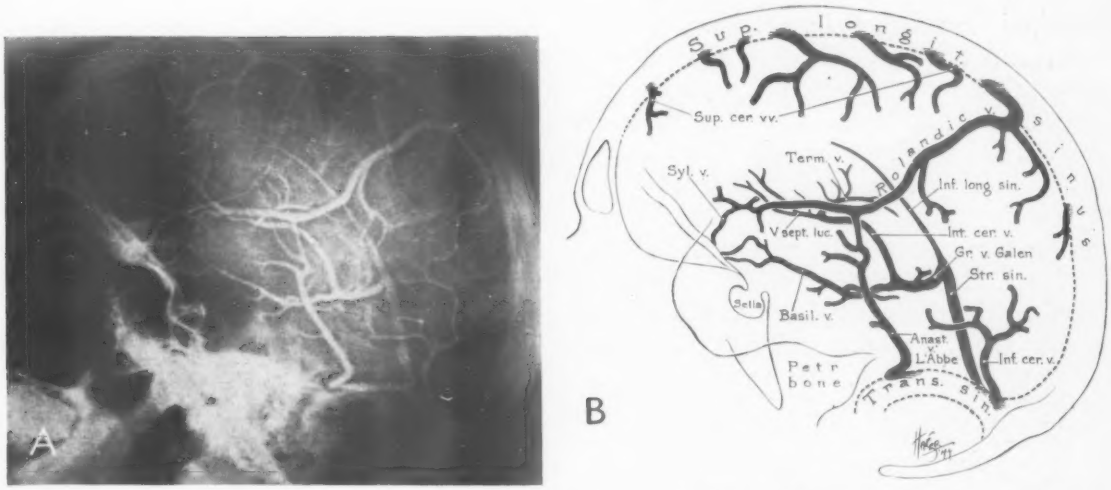

Fig. 7. (*A*) Lateral view of the normal carotid angiogram (venous filling). Note characteristic position and configuration of deep cerebral veins and sharp angle at which vein of Galen joins straight sinus. (Retouched.) (*B*) Drawing of (*A*). The main sinuses, superficial and deep cerebral veins are labelled.

and marks the division between the inferior longitudinal and the straight sinuses. The dural sinuses visualized by angiography consist of the superior longitudinal sinus, the inferior longitudinal and straight sinuses and the paired transverse sinuses. All of these sinuses lie entirely within the dura mater and are midline structures except for the paired transverse sinuses which extend laterally across the occipital bone.

Before this general discussion of the vascular anatomy of the brain is completed, it may be well to direct our attention briefly to the anatomy of the external carotid artery and its branches. This system sometimes fills during angiography and the resulting pattern may be confused with that of the internal carotid system.

The external carotid artery courses upward in the neck and divides into three

Fig. 8. Anteroposterior view of the normal carotid angiogram (venous filling). Note superimposition of venous sinuses and internal cerebral vein. There is ipsilateral filling of the deep and superficial cerebral veins with filling of superior and inferior longitudinal sinuses, the straight sinus, and both transverse sinuses.

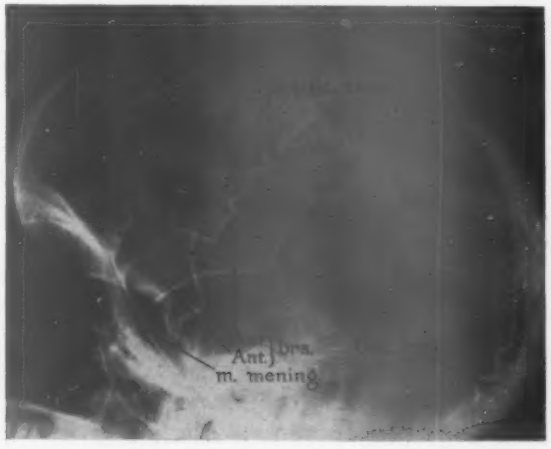

Fig. 9. Lateral view of normal carotid angiogram (arterial filling) to illustrate the branches of the external carotid artery. The point of the needle was in the external carotid artery and there is no filling of the internal carotid artery and its branches. The branches of the external carotid artery which are of angiographic interest are labelled. (Retouched.)

principal branches (Fig. 9). Two of these branches, the superficial temporal and occipital, supply the scalp, whereas the other branch, the middle meningeal, enters the cranial cavity through the foramen spinosum and then courses laterally and superiorly along the inner table of the skull to supply the dura mater. As we shall see later, the courses of these vessels are significantly different from those of the internal carotid system and with reasonable care may be distinguished from it.

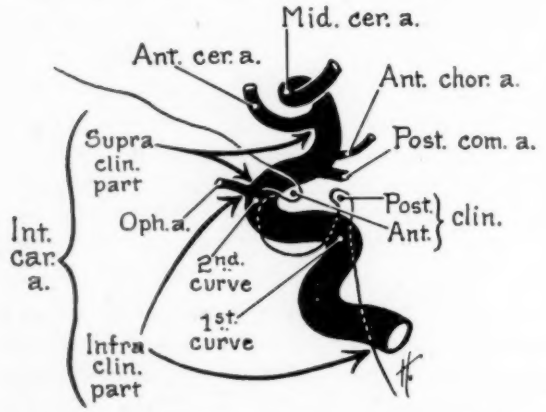

FIG. 10. Schematic drawing of lateral view of intracranial portion of internal carotid artery. The infraclinoid and supraclinoid portions of the internal carotid artery are illustrated, and the first and second curves of the infraclinoid portion of the internal carotid artery are labelled.

ANGIOGRAPHY

Most angiography of the skull is performed in the lateral and anteroposterior projections. In the following paragraphs we shall discuss the normal roentgenologic relationships of the cerebral vessels first from the lateral viewpoint and then from the perspective of the anteroposterior films. We have further organized these discussions so that attention is first directed to normal roentgen anatomy, then to anatomical variations and finally to physiological variations. By the term, physiological variation, is meant any abnormality of filling that is created by a disturbance of normal physiology, such as spasm of a vessel during the injection of the opaque material.

A. Arterial System

INTERNAL CAROTID ARTERY.

Lateral Projection.

(a) Roentgen Anatomy. The anatomy of the intracranial portion of the internal carotid artery is shown in Figure 10. In the lateral projection that portion of the carotid artery entering the skull through the carotid canal is poorly demonstrated since it is seen end-on. From this point, however, the course of the artery can be easily followed. The internal carotid artery emerges from the foramen lacerum, pierces the external layer of the dura mater, and runs superiorly and slightly medially along the lateral surface of the body of the sphenoid bone. When it reaches the dorsum sellae, it makes a sharp turn anteriorly and courses for a short distance to a position just beneath the anterior clinoid process where it curves back on itself and forms a groove along the inferior border of the anterior clinoid process. These portions of the artery adjacent to the sphenoid bone are intracavernous and lie near the pituitary gland.

In the region of the anterior clinoid process the internal carotid artery pierces the internal layer of the dura mater. It then runs posteriorly for a short distance, turns superiorly and may then bifurcate into its terminal branches; more often, however, it curves back on itself and again courses anteriorly a short distance before bifurcating (Fig. 12*A*). Egas Moniz[3] has used the term "carotid siphon" for the curved intracranial portion of the internal carotid artery, and he uses the terms "single," "transitional," or "double" to indicate the degree of tortuosity of the supraclinoid portion of the carotid artery.

For purposes of description, it is convenient to divide the internal carotid artery into infraclinoid and supraclinoid portions. The infraclinoid portion constitutes that section of the artery which extends from the foramen lacerum to the anterior clinoid process; the supraclinoid portion is that section of the artery beyond.

The infraclinoid portion may be further divided into first and second curves (Fig. 10). The first curve, or more proximal segment, lies in the region of the dorsum sellae; the second, or more distal, segment constitutes the sharply curving section which lies immediately beneath the anterior clinoid process (Fig. 10).

The infraclinoid portion of the carotid artery gives rise to ophthalmic, posterior communicating, and anterior choroidal branches (Fig. 1*A* and *B*, and 10). The ophthalmic artery arises from the internal carotid artery just proximal to the anterior clinoid process and passes anteriorly below the optic nerve to enter the orbital cavity through the optic foramen. On entering the orbit it follows the course of the optic nerve and lies about 1 cm. below the orbital roof. The next branch, the posterior communicating artery, will be discussed under the basilar system. Finally, the anterior choroidal artery, which always originates several millimeters distal to the posterior communicating artery, courses posteriorly (Fig. 1*A* and *B*) to supply the choroid plexus, the hippocampus and portions of the globus pallidus and the internal capsule. Small arterial twigs from the carotid siphon, which supply the walls of the cavernous sinus and pituitary gland, are usually not identified on the cerebral angiogram and hence are not of importance here.

(b) Anatomical Variations. The diameter of the internal carotid artery usually varies between 3 and 5 mm. A rare, but very important anomaly is absence of the vessel. Lourey[16] reported a case of unilateral absence of the internal carotid artery with no evidence of a carotid canal in the petrous bone. In this case, the middle cerebral artery arose from the posterior communicating artery and the anterior cerebral artery received its blood supply from the opposite internal carotid artery. Dandy[17] reported absence of the left internal carotid artery in a sixteen year old girl who also had congenital absence of the orbital roof. Fisher[8] reported bilateral absence of the internal carotid arteries in a thirty-nine year old male who died from cerebral hemorrhage. He believed that the principal anastomosis in this case was between terminal branches of the posterior and middle cerebral arteries. Another rare type of anomaly is one reported by Quain[18] in which an anomalous branch of the left internal carotid artery perforates the sphenoid bone and conects with the basilar artery.

The course of the internal carotid artery frequently presents a number of significant variations. Some of these may be erroneously interpreted as displacement of the carotid artery by such patholoy as an intrasellar, parasellar, or suprasellar mass. The first curve of the infraclinoid portion of the carotid artery probably demonstrates the greatest variation in configuration and position (Fig. 11*A*, 12*A*, 13*A* and 14*A*). It will be noted in some of these illustrations that the carotid artery extends superiorly as far as the posterior clinoid process and occasionally extends above this level. This marked tortuosity is well demonstrated both in the lateral and anteroposterior angiograms.

Since arterial tortuosity is often associated with aging processes we have examined the relationship between this finding and the age of the patient; the results of this study are shown in Table 1. These

Table I

Degree of Tortuosity	Present In	Age of Patient in Years	
		Youngest	Oldest
None	48%	18	55
Slight	16	6	44
Moderate	24	10	58
Marked	12	38	71

figures seem to demonstrate that in most cases carotid tortuosity is not associated with age but that it is a developmental variant. Old age and accompanying arteriosclerotic changes only increase the degree of tortuosity which is already present.

The second curve of the infraclinoid portion of the carotid artery (Fig. 11*A*,

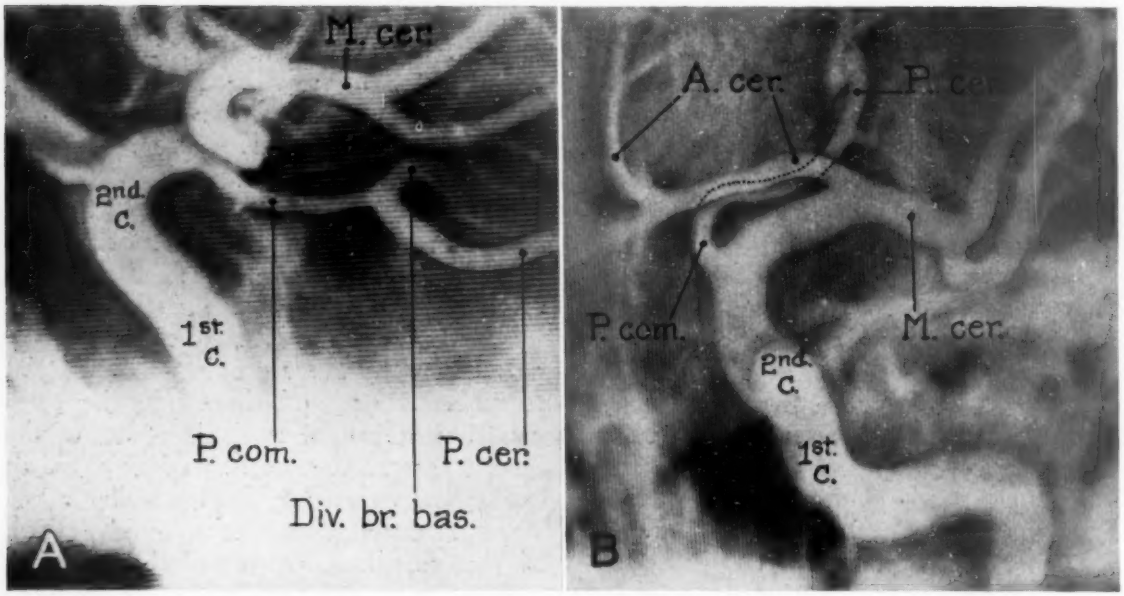

Fig. 11–14. Views of intracranial portion of internal carotid artery (arterial filling).
Fig. 11. Lateral (*A*) and anteroposterior (*B*) views of normal carotid angiogram (arterial filling). Illustrates minimal tortuosity of infraclinoid portion of internal carotid artery. Posterior communicating and posterior cerebral arteries are filled. (Retouched.)

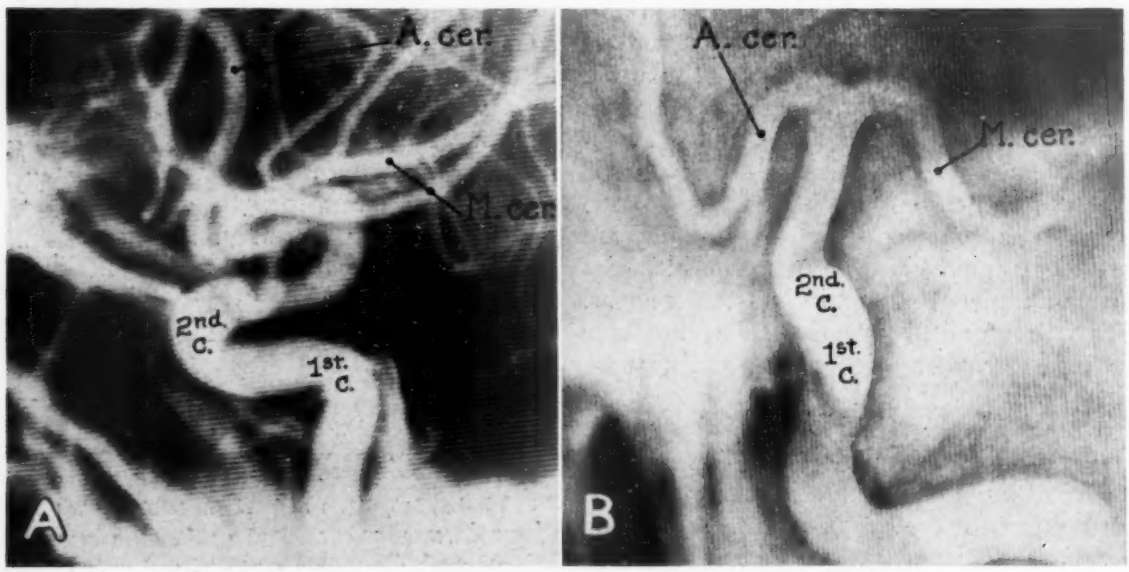

Fig. 12. Lateral (*A*) and anteroposterior (*B*) views of normal carotid angiogram (arterial filling). There is slight tortuosity of infraclinoid portion of internal carotid artery. The internal carotid artery courses anteriorly before bifurcating. Note appearance of bifurcation in anteroposterior view. (Retouched.)

12*A*, 13*A*, and 14*A*) shows much less variation than the first. However, there appears to be some correlation between the shape of the first curve and the shape of the second curve in that the latter segment is usually full when the first curve is tortuous. Furthermore, the second curve often appears somewhat angulated when the first is not tortuous (Fig. 11*A*, 12*A*, 13*A*, and 14*A*).

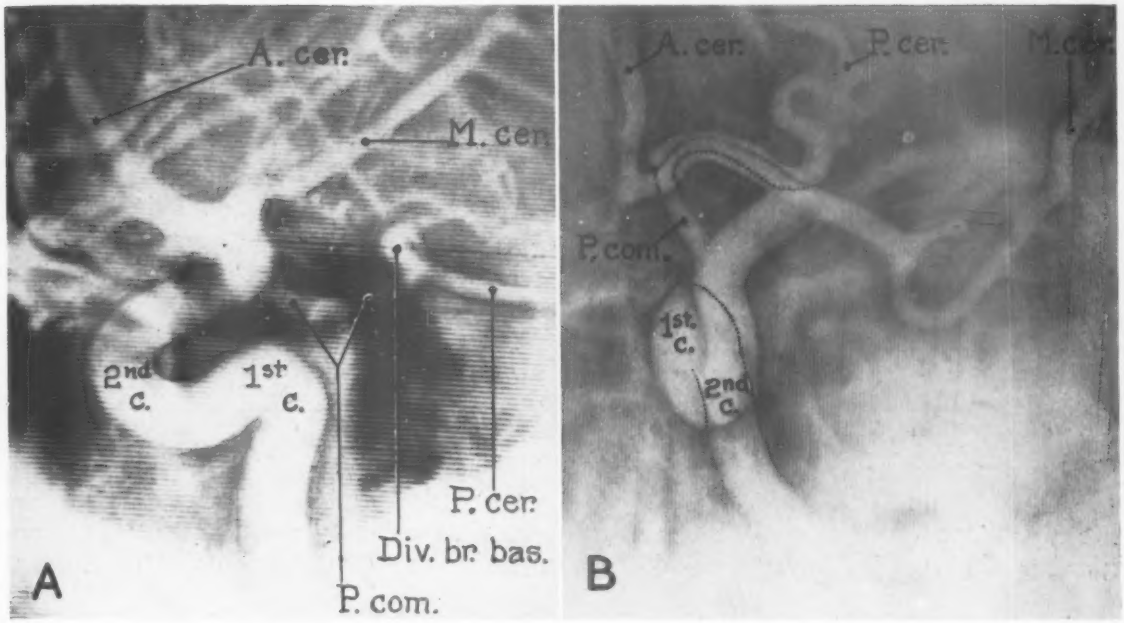

Fig. 13. Lateral (*A*) and anteroposterior (*B*) views of normal carotid angiogram (arterial filling). There is moderate tortuosity of infraclinoid portion of internal carotid artery. (Retouched.)

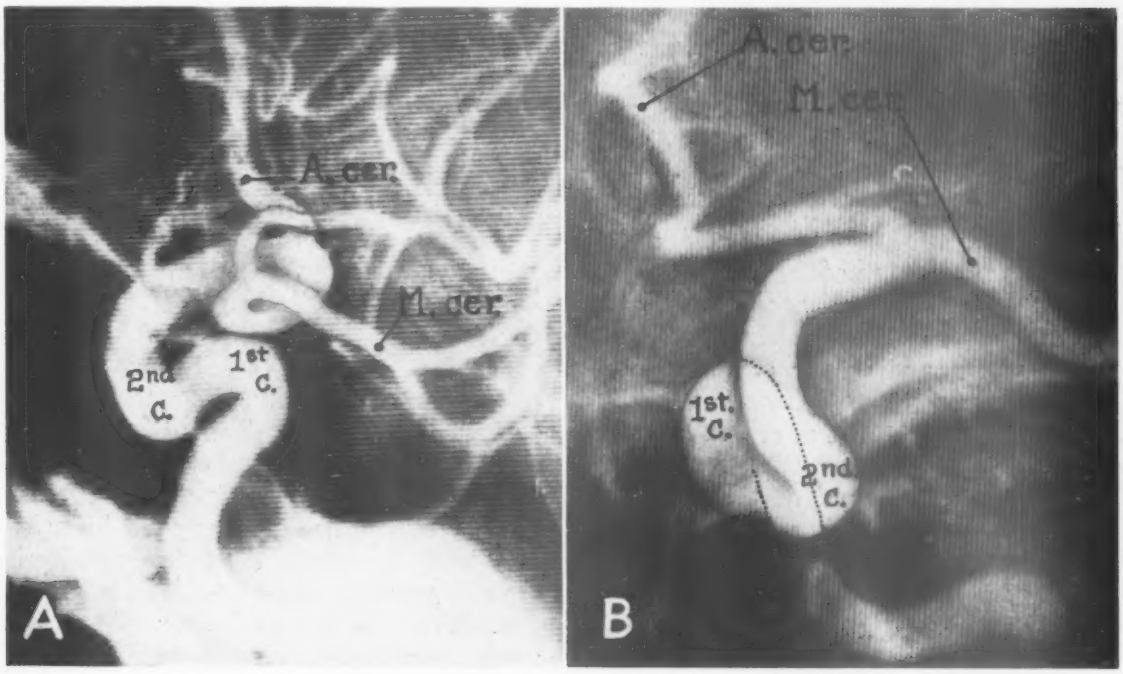

Fig. 14. Lateral (*A*) and anteroposterior (*B*) views of normal carotid angiogram (arterial filling). There is marked tortuosity of infraclinoid portion of internal carotid artery. (Retouched.)

The supraclinoid portion of the internal carotid artery presents great variation in position, length, and curvature. The proximal segment lies immediately above the horizontal plane of the diaphragma sellae. As the artery courses posteriorly it may lie at the level of the posterior clinoid process or 2 to 4 mm. superior to it. Since intrasellar

tumors can cause upward displacement of this portion of the carotid artery, it is sometimes difficult to differentiate pathological change from a normal configuration.

The internal carotid artery may bifurcate above the posterior clinoid process, may course anteriorly for a variable distance and then bifurcate, or may double back on itself again and travel a short distance posteriorly before dividing (Fig. 11*A*, 12*A*, 13*A* and 14*A*). Although all three variations are common, our experience corresponds with that of other authors who have found that the "single" carotid siphon occurs most frequently, followed by the "double" and then the "transitional." No correlation appears to exist between the number of curves in the supraclinoid portion of the internal carotid artery and the degree of tortuosity of the infraclinoid portion

When present, the distal segment of the supraclinoid portion of the carotid artery may parallel the course of the proximal segment, be superimposed on it, or be separated from it by a distance up to 10 mm. (Fig. 12*A*). This latter variation may be difficult to differentiate from downward displacement caused by a tumor.

The branches of the internal carotid artery present a reasonably consistent appearance. In our series the ophthalmic artery could be identified in 98 per cent of the cases, and in the one instance in which it was not seen, the cause was probably technical. This artery (Fig. 1*A*) always occupied a position corresponding to that of the optic nerve and displacement was never observed except in the presence of an orbital mass. The artery may sometimes be difficult to see because with slight rotation of the head it may be superimposed on the opposite orbital roof, and thus be obscured.

Although absence of the anterior choroidal artery (Fig. 1*A*) has never been reported, it could be visualized in only 84 per cent of our cases. This was possibly due to the fact that the vessel is small and therefore is recorded on the films with great difficulty. Stereoscopic films are of great value in its identification because it lies near the midline and can be differentiated from other arteries which lie more superficially. Its course is fairly straight except for slight deviations due to tortuosity. From its origin it runs almost directly posteriorly to the position of the shadow of the pineal gland. Its position may roughly be determined by drawing a line from its origin to the pineal gland, which is often calcified. Displacement of the anterior choroidal artery may be the *only* angiographic sign of a thalamic tumor.

(c) Physiological Varaitions. Bilateral filling of the internal carotid artery with unilateral injection may occur when the anterior communicating artery is sufficiently large to allow filling of the contralateral carotid system. This occurred in one of our cases (Fig. 28) and is discussed in detail under physiological variations of the middle cerebral artery.

Spasm which was sufficiently marked to completely occlude the internal carotid artery for a period of at least five seconds was noted in several of our patients (Fig. 15*A* and *B*), although there are few references to this finding in the literature. Hodes, Perryman and Chamberlain[12] state that they, too, have seen several cases of transient vascular spasm in which the anterior and middle cerebral arteries did not fill even though the internal carotid artery was opacified. They believe that this phenomenon should not be interpreted as occlusion of the vascular system unless it can be demonstrated on several injections. From our experience it appears that spasm of the internal carotid artery or its branches may be interpreted if the following criteria are present:

1. On at least one injection of the contrast medium there is good opacification of the internal carotid artery up to the point of its bifurcation and this opacification persists for a period of five seconds with little or no contrast medium entering the anterior or middle cerebral artery.

2. On at least one injection of the contrast medium none remains in the internal carot-

id artery and there is good filling of the anterior and middle cerebral arteries.

One of our cases strikingly fulfilled these criteria. This was a fifty-two year old white man who was operated on for an orbital mass which proved to be an inflamed lacrimal gland. During both injections, in the lateral projection, there was normal filling of the anterior and middle cerebral arteries and no abnormality was seen in the intracranial portion of the internal carotid artery. During the first injection in the anteroposterior projection, however, the internal carotid artery was well opacified to the point of its bifurcation for a period of five seconds, but neither the anterior nor the middle cerebral artery was visualized. This spasm caused a temporary anoxia of the brain and a contralateral transient hemiplegia.

When the carotid injection has been made on the left side, we have sometimes observed a transient aphasia of the patient. This latter finding occasionally has occurred where there was no angiographic evidence of spasm of the carotid artery; it is conceivable, however, that spasm may have occurred between injections or even after the procedure was finished. Aside from the effects produced by cerebral anoxia, arterial spasm is important because if several injections of the internal carotid artery are not made, the anterior and middle cerebral arteries may not be visualized and an incorrect diagnosis of occlusion or thrombosis may be made.

The cause of vascular spasm is not known. It is possibly related directly or indirectly to the injection of the contrast medium. Although our instances of spasm occurred after the use of 35 per cent diodrast, Hodes, Perryman and Chamberlain[12] observed the phenomenon when thorotrast was injected. One type of contrast material is not therefore responsible for the finding. Spasm may be related to the extravasation of contrast medium into the soft tissues. We know that such leakage did occur in several of our cases but slight extravasation has occurred many other times without producing this effect. The phenomenon usually appears during the second, third, or fourth injection and only rarely during the first injection.

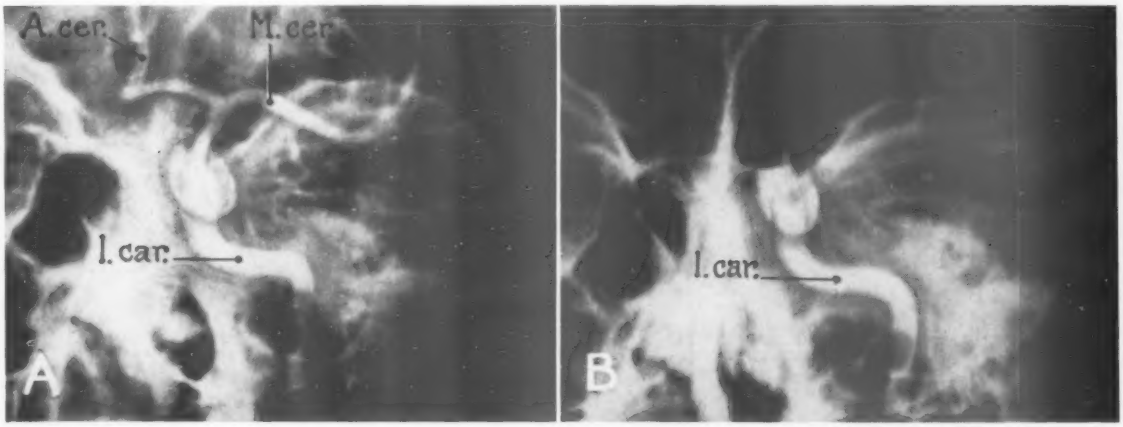

Fig. 15 (*A*) and (*B*). Anteroposterior views of carotid angiogram on same patient (arterial filling). In (*A*) there is normal filling of anterior and middle cerebral arteries, but in (*B*), which was taken after the next injection, the anterior and middle cerebral arteries are not filled although the internal carotid artery is well filled. This film was taken five seconds after the injection of diodrast and there has been no change from a film which was taken immediately after the injection. (Retouched.)

Anteroposterior Projection.

(a) Roentgen Anatomy. The course of the internal carotid artery can be easily followed in this projection (Fig. 11*B*, 12*B*, 13*B* and 14*B*). After running medially

through the carotid canal the artery turns superiorly rather abruptly and ascends along the body of the sphenoid bone. The first curve of the infraclinoid portion of the artery is superimposed on itself and the appearance is a little more confusing than in the lateral projection. The second curve usually lies slightly medially to the first curve. This part of the artery courses inferiorly to the anterior clinoid process and is separated from the opposite internal carotid artery by the width of the body of the sphenoid bone. The supraclinoid portion of the artery extends posteriorly and slightly laterally. The bifurcation of the artery, seen in the anteroposterior view, therefore, is lateral to the second curve of the infraclinoid portion. The appearance of the bifurcation depends on the type of the carotid siphon.

The ophthalmic artery and anterior choroidal artery are not usually identified in the anteroposterior projection because they are projected almost end-on and are superimposed on bony structures. The appearance of the posterior communicating artery will be discussed later.

(b) Anatomical Variations. There is considerable variation in the appearance of the first curve of the infraclinoid portion of the carotid artery in this projection (Fig. 11*B*, 12*B*, 13*B* and 14*B*). It will be noted that when there is marked tortuosity of the first curve, the superimposed portions of this curve give the appearance of a round vascular mass or may even present the appearance of a circle. The first curve is usually lateral to the second curve but sometimes they may be the same distance from the midline; not infreqently a part of the first curve may lie medially to the second curve. This variation in position makes it difficult to determine when there is lateral displacement of the first curve by an intrasellar mass.

As noted before, there is much less variation in the course of the artery's second curve than of the first. Since this portion of the artery always runs in a groove inferiorly to the anterior clinoid process, its distance from the midline depends on the width of the sphenoid bone. In our series of cases the distance from the second curve to the midline varied from 0.5 to 1.0 cm. and this portion of the artery was usually closer to the midline than any other segment. The supraclinoid portion of the internal carotid artery always lies several millimeters lateral to the anterior clinoid process.

The appearance of the internal carotid artery at its bifurcation depends on the form of the carotid siphon (Fig. 11*B*, 12*B*, 13*B* and 14*B*). With the "single" type, the bifurcation is somewhat T-shaped in appearance. With the "double" type the proximal parts of the anterior and middle cerebral arteries appear depressed below the plane of the bifurcation. This appearance is caused by projection and is due to the fact that the bifurcation is slightly posterior to the proximal parts of these arteries.

ANTERIOR CEREBRAL ARTERY.

Lateral Projection.

(a) Roentgen Anatomy. The proximal portion of the anterior cerebral artery extends from the bifurcation of the internal carotid artery to the origin of the anterior communicating artery. This portion of the anterior cerebral artery is difficult to visualize in the lateral projection because it is seen end-on and is better studied in the anteroposterior projection. Its discussion will therfore be postponed to later paragraphs.

Beyond the origin of the anterior communicating artery, the anterior cerebral artery (Fig. 1*A* and *B*) ascends superiorly between the cerebral hemispheres and lies a short distance anteriorly to the lamina terminalis. This vertical portion of the anterior cerebral artery gives off a rather constant branch called the frontopolar artery, which also runs between the cerebral hemispheres. This frontopolar artery occupies a position anterior to the anterior cerebral artery, however, and at times lies very close to the inner table of the skull. The medial striate artery, another branch

of the anterior cerebral artery, is usually not recognized on the cerebral angiogram. The final portion of the anterior cerebral artery courses posteriorly around the genu of the corpus callosum and then runs along the superior surface of the corpus callosum to the splenium. This horizontal portion of the anterior cerebral artery is called the pericallosal artery because of its relationship to the corpus callosum. There is also an inconstant branch called the callosal-marginal artery which usually arises at the genu of the corpus callosum but may arise from the vertical portion of the anterior cerebral artery (Fig. 1*A* and *B*). In place of the callosal-marginal artery several small branches arising from the pericallosal artery may be found. These branches lie in the cingulus sulcus and run closely together about 1 cm. superior to and parallel to the course of the pericallosal artery. The branches of the anterior cerebral artery supply the medial portions of the frontal and parietal lobes and anastomose with subdivisions of the middle cerebral artery.

(b) Anatomical Variations. The anterior cerebral artery varies in diameter from 1 to 3 mm. in its vertical portion. Differences in the sizes of the two anterior cerebral arteries are common and Egas Moniz[3] gives measurements showing the variations which may occur in different portions of the vessels.

Complete absence of an anterior cerebral artery is extremely rare although it is not uncommon for there to be a single anterior cerebral artery which supplies both cerebral hemispheres. Anatomists have long recognized that the anterior cerebral arteries sometimes fuse. In Windle's[23] series of 200 cases he found an incidence of 0.5 per cent where there was complete fusion and 4.0 per cent where there was partial fusion of the vessels. Egas Moniz[3] also described cases in which this took place and in one case in our series this apparently occurred. Bilateral carotid angiography was performed in this patient and there appeared to be only one large anterior cerebral artery which was supplied by both internal carotid arteries and which sent branches to both cerebral hemispheres.

Separate consideration must be given to the proximal anterior cerebral artery since changes in size or even absence of this portion may occur independently of any change in the more distal portions of the artery. Variation in size of the proximal anterior cerebral artery is very frequent and this vessel often has a lumen of only 1 mm. in diameter. Egas Moniz and Almeida[3] report 2 cases in which the proximal anterior cerebral artery was only a small twig. In a series of 200 autopsied cases Windle[23] described 1 case with a thread-like proximal anterior cerebral artery. In a series of autopsied cases which we have studied, 1 case was encountered in which there was a complete absence of the left proximal anterior cerebral artery, and the left anterior cerebral artery, which was of normal size, received its blood supply from the opposite anterior cerebral artery through the anterior communicating artery. Absence of the proximal anterior cerebral artery has not been noted in our series of angiograms since there has always been filling of the anterior cerebral artery on at least one injection. Although diminished size or absence of the proximal anterior cerebral artery is not common, this anomaly is important since carotid angiography on that side will show no filling of the vessel and therefore will lead possibly to the diagnosis of pathological occlusion. Other factors producing non-filling of the anterior cerebral artery will be discussed later.

Since the anterior communicating artery unites the two anterior cerebral arteries, it is appropriate to discuss its variations at this time. The anterior communicating artery may consist of one or several branches which have a diameter of 0.5 to 3.0 mm. Egas Moniz and Almeida[3] have never seen a case with complete absence of this communicating branch and speculate that if it were not present, there would be varying degrees of fusion of the anterior cerebral arteries. Of a total of 1,803 autopsied cases reported in the literature,

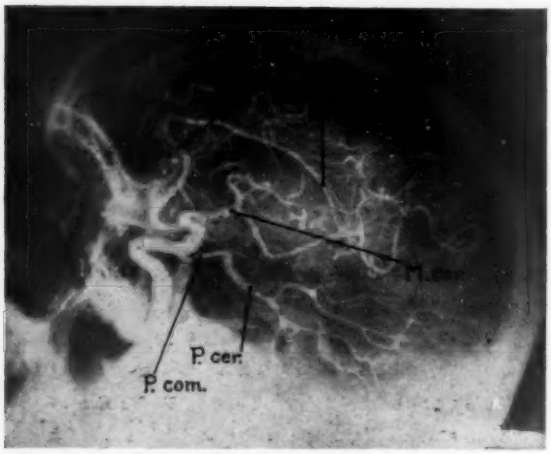

Fig. 16. Lateral view of the normal carotid angiogram (arterial filling). Both anterior cerebral arteries fill. Note marked tortuosity of vertical portion of anterior cerebral arteries. Pericallosal artery lies close to corpus callosum. Posterior communicating and posterior cerebral arteries are filled.

Dandy[17] found 3 cases in which the anterior communicating artery was said to be absent. It is quite evident that absence of the anterior communicating artery is an extremely rare anomaly although variations in size are common. The anterior communicating artery cannot usually be identified on the cerebral angiogram in either the lateral or anteroposterior projections, but its presence is sometimes manifested by filling of both anterior cerebral arteries.

The anterior cerebral artery distal to the anterior communicating artery is clearly seen in the lateral projection. Considerable variation exists in the course of the vertical portion of the artery (Fig. 16, 17, 18, 19, 20, 21 and 1*A*). It may lie adjacent to the lamina terminalis and clearly show the position of this structure or it may lie some distance anteriorly. In our series of cases, the distance between the vertical portion of the anterior cerebral artery and the inner table of the skull ranged from 0.5 cm. to 2.0 cm.

As the anterior cerebral artery rounds the genu of the corpus callosum, the same variation in position is evident. Measurements from this portion of the artery to the inner table of the skull in the anterior fossa ranges from 1.5 to 2.5 cm. Thus, the vertical portion of the anterior cerebral artery is an unreliable landmark for determining the exact position of the lamina terminalis and genu of the corpus callosum. In general, the portion of the artery adjacent to the genu has an angulated appearance as shown in Figure 18.

As previously indicated, the anterior cerebral artery, after rounding the genu, courses posteriorly and roughly outlines the corpus callosum. Emphasis should be placed on the fact that although the pericallosal artery runs superiorly to the corpus callosum, it does not usually show the exact position of the corpus callosum (Fig. 19 and 21). Furthermore, it will often lie as much as 1.0 cm. above this structure for a part of its course. Despite the tortuosity and variation in its position, however, the terminal branches of the pericallosal artery almost invariably lie adjacent to the splenium of the corpus callosum and accurately localize its position (Fig. 21).

The frontopolar artery always courses anteriorly to the anterior cerebral artery and although there is some variation in its course, it usually runs closer to the inner table of the skull than to its parent vessel.

The inconstant callosal-marginal artery (Fig. 1*A* and *B*, 18 and 21) appeared as a distinct vessel in 56 per cent of our cases.

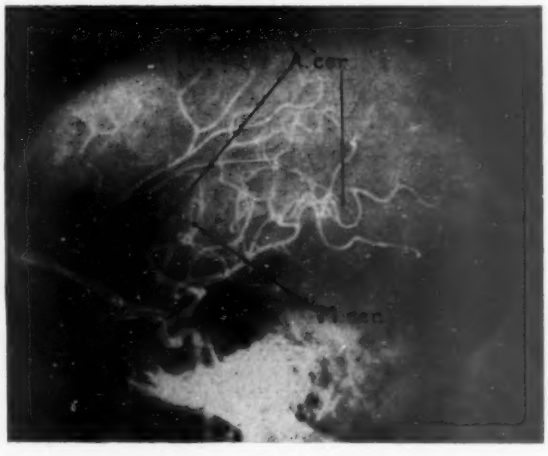

Fig. 17. Lateral view of the normal carotid angiogram (arterial filling). Vertical portion of anterior cerebral artery forms a sharp angulation as it turns posteriorly. Proximal portion of ascending frontoparietal artery lies anteriorly to proximal portion of middle cerebral artery. (Retouched.)

It is usually described as arising from the anterior cerebral artery in the region of the genu of the corpus callosum (Fig. 21). Although it did arise in this location in 80 per cent of our cases in which it was identified, in 20 per cent it arose from the lower part of the vertical portion of the anterior cerebral artery and was sometimes difficult to distinguish from the opposite anterior cerebral artery (Fig. 19), unless there was filling of both vessels.

When the callosal-marginal branch is absent, the anterior cerebral artery often gives rise to several small branches which run together in the cingulus sulcus parallel to the pericallosal artery. Because of superimposition these vessels frequently give the appearance of one distinct artery. In those cases in which the pericallosal artery is tortuous and occupies the cingulus sulcus for a part of its course, the pericallosal and callosal-marginal arteries will be superimposed for a part of their courses (Fig. 21). The callosal-marginal artery may run in the cingulus sulcus for most of its course or may leave this sulcus after a short distance and run more superiorly on the medial surface of the cerebral hemisphere (Fig. 21).

When the vertical portions of the anterior cerebral arteries are visualized simultaneously on the two sides of the brain, it will usually be observed that they follow much the same course. Egas Moniz[3] was probably the first to make this observation and also noted that, of all the cerebral vessels, the pericallosal branches of the anterior cerebral arteries constitute the only vascular structures which pursue similar courses on both sides with but slight variation. Of our group of cases, 46 per cent showed filling of both anterior cerebral arteries in the lateral projection. In all cases the vertical portions of the anterior cerebral arteries were identical in position or not separated more than 3 mm. However, the courses of the pericallosal arteries (Fig. 21) were identical in only 80 per cent; in the remaining 20 per cent the courses varied as much as 10 mm., with one pericallosal artery lying against the corpus callosum and the other running in the cingulus gyrus (Fig. 19) in 1 case.

Our experience indicates that the callosal-marginal artery may be easily confused with the opposite anterior cerebral

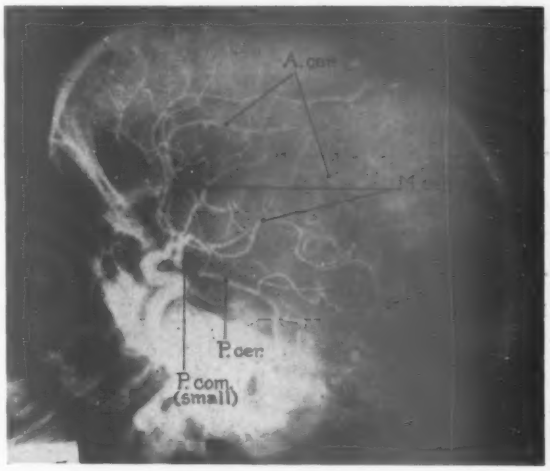

Fig. 19. Lateral view of the normal carotid angiogram (arterial filling). Both anterior cerebral arteries fill. Note that one pericallosal artery courses about 7 mm. superiorly to the other pericallosal artery in the region of the genu of the corpus callosum. One callosal-marginal artery arises from the vertical portion of the anterior cerebral artery and simulates the opposite anterior cerebral artery which is not clearly seen in this case because of superimposition of the two anterior cerebral arteries. The posterior communicating and posterior cerebral arteries fill. (Retouched.)

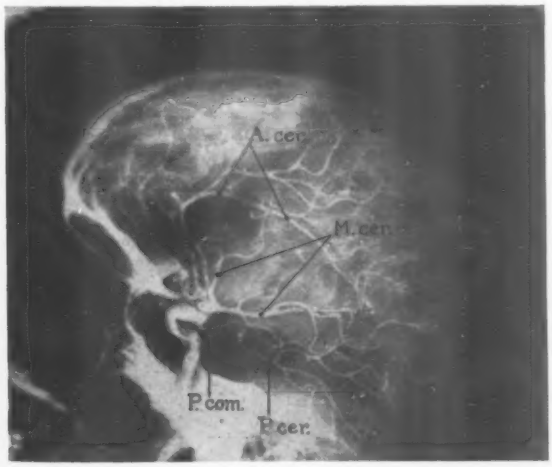

Fig. 18. Lateral view of the normal carotid angiogram (arterial filling). Both anterior cerebral arteries fill. Vertical portion of anterior cerebral artery shows minimal tortuosity. Posterior communicating artery is rather small but the posterior cerebral artery fills. (Retouched.)

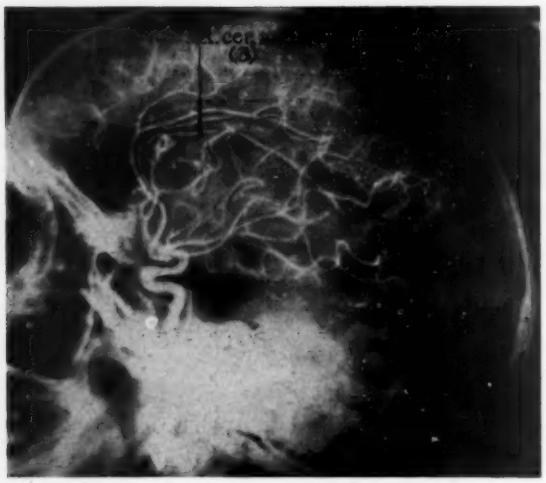

Fig. 20. Lateral view of the normal carotid angiogram (arterial filling). Both anterior cerebral arteries fill and both pericallosal and callosal-marginal arteries can be identified. There is an additional artery in the region of the pericallosal arteries which lies immediately adjacent to the corpus callosum. This artery is probably the middle anterior cerebral artery. (Retouched.)

artery. It seems probable that some of the cases reported in the literature as showing marked variation in distance between the vertical portions of the two anterior cerebral arteries actually represented filling of only one anterior cerebral artery and of an anomalous callosal-marginal artery.

A middle anterior cerebral artery has been described by Windle.[23] This vessel arose from the anterior communicating artery and followed the general course of the anterior cerebral artery. Its course differed from the latter, however, in that it followed the superior surface of the corpus callosum very closely and accurately outlined this structure. Windle reported this artery to be present in 4.5 per cent in his 200 autopsied cases. Egas Moniz and Almeida[3] reported its occurrence in 10 per cent of their autopsied material, but did not state how often it could be identified on cerebral angiograms. They reported that it arose from either the anterior communicating artery or from one of the anterior cerebral arteries. The probable reason why this artery has not been mentioned more often in the literature of cerebral angiography is that it is usually superimposed throughout most of its course on the anterior cerebral arteries. We have identified it in one autopsied case and have one cerebral angiogram (Fig. 20) in which it can readily be seen because the filled pericallosal arteries run in the cingulus sulcus, and therefore are not superimposed on it. In several other cases there is suggestive evidence of the presence of a middle anterior cerebral artery but the evidence is not clear because of superimposition of the anterior cerebral arteries. Recognition of this anomalous branch is important for two reaons: first, it can be mistaken for the opposite anterior cerebral artery, and second, it accurately outlines the position of the corpus callosum.

(c) Physiological Variations. Failure of filling of the anterior cerebral artery on the side of the injection occurs not infrequently and has been interpreted by some workers to be due to occlusion of the vessel. Other investigators, however, believe that this diagnosis must be made with great caution since the artery may fill during one injection and not during the next. The factors which prevent filling of the anterior cerebral artery are poorly understood. Egas

Fig. 21. Lateral view of the normal carotid angiogram (arterial filling). Both anterior cerebral arteries fill and the pericallosal and the callosal-marginal arteries on each side are well shown. The terminal portions of the pericallosal arteries are well demonstrated.

Moniz[3] found difficulty in visualizing the vessel when he ligated the common carotid artery proximal to the site of injection, and from this concluded that diminished pressure in the carotid system may be of considerable importance in causing the phenomenon.

In our series of cases, the anterior cerebral artery always filled on the side of injection during some period of the angiographic procedure. However, in 4 per cent of the cases, filling did not occur during one of the injections. Apparently, vascular spasm with subsequent reduction of the pressure within the carotid system was responsible for these observations. These cases serve to illustrate that caution must be excerised in making a diagnosis of occlusion of the anterior cerebral artery. Furthermore, if the vessel cannot be visualized after several injections, the opposite carotid artery should be injected since both anterior cerebral arteries are supplied by one internal carotid artery when the proximal anterior cerebral artery on one side is small or absent.

A review of the literature indicates that filling of both anterior cerebral arteries is common. In our experience this occurred in 46 per cent of the cases (Fig. 21). Filling of the opposite anterior cerebral artery is determined by the size of the anterior communicating artery and the ipsilateral increase in the pressure of the anterior cerebral artery due to the force of the injection. Other factors which decrease the pressure in the opposite anterior cerebral artery also may play a role in this phenomenon.

Anteroposterior Projection.

(a) Roentgen Anatomy. The proximal portion of the anterior cerebral artery is clearly seen from the point of bifurcation of the internal carotid artery until it unites with the anterior communicating artery (Fig. 11*B*, 12*B*, 13*B*, 14*B*). It runs medially in the reverse direction to the middle cerebral artery and lies at the same level as the bifurcation of the internal carotid artery. In some cases it appears to be depressed below the level of the bifurcation but this is due to projection. The remainder of the anterior cerebral artery (Fig. 2*A* and *B*) lies in the midline of the skull except for minor deviations due to tortuosity. The different branches of the anterior cerebral artery cannot be clearly identified in the anteroposterior view because of superimposition of one on another. Since the anterior cerebral artery lies in the midline between the two cerebral hemispheres, it is a valuable indicator of lateral shift of the cerebral hemispheres.

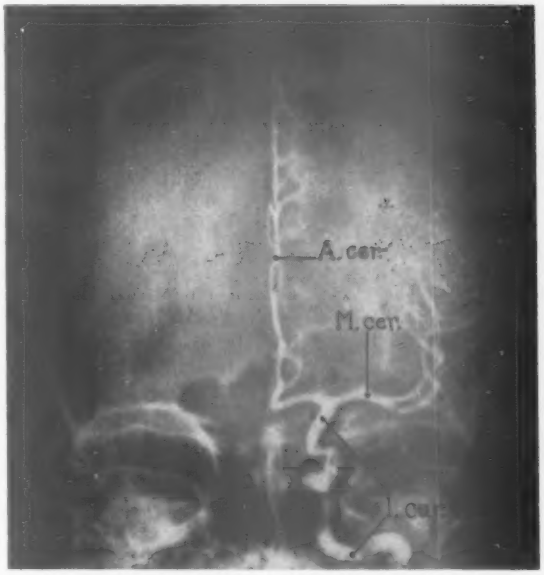

Fig. 22. Anteroposterior view of the normal carotid angiogram (arterial filling). No deviation of the anterior cerebral artery. (Retouched.)

(b) Anatomical Variations. The anterior cerebral artery is usually located within 4 mm. of the midline; tortuosity of the artery sometimes causes greater displacement, however (Fig. 22, 23 and 24). Table II lists the deviations from the midline which

Table II

Deviation from Midline—not over	Percentage of cases
2 mm.	42
4 mm.	46
6 mm.	8
8 mm.	2
10 mm.	2

Fig. 23. Anteroposterior view of the normal carotid angiogram (arterial filling). Moderate deviation of the anterior cerebral artery due to tortuosity. (Retouched.)

Fig. 24. Anteroposterior view of the normal carotid angiogram (arterial filling). Marked deviation of the anterior cerebral artery due to tortuosity. (Retouched.)

we have observed in the anterior cerebral arteries of our cases.

(c) Physiological Variations. Absence of filling or bilateral filling of the anterior cerebral arteries is easily seen in this projection. Factors producing these changes have been discussed.

MIDDLE CEREBRAL ARTERY.

Lateral Projection.

(a) Roentgen Anatomy. From its origin at the bifurcation of the internal carotid artery, the middle cerebral artery proceeds laterally deep in the sylvian fissure separating the temporal and parietal lobes. Because the proximal portion of the middle cerebral artery is seen end-on in the lateral projection, it is difficult to follow without stereoscopic views (Fig. 1*A*). This portion of the middle cerebral artery may run at the same level as the bifurcation of the internal carotid artery, but usually courses at a level several millimeters below it (Fig. 14*A*). Immediately before the middle cerebral artery turns posteriorly in the sylvian fissure, it gives off a rather prominent and fairly constant branch called the ascending frontoparietal artery (Fig. 1*A* and *B*). This artery can usually be identified without difficulty except for its proximal portion which is rather tortuous and is often superimposed on the middle cerebral artery. Sometimes the proximal part of the frontoparietal artery curves anteriorly to the middle cerebral artery and may be mistaken for the middle cerebral artery itself (Fig. 17). The ascending frontoparietal artery characteristically divides into three terminal branches which have been described as having the appearance of a candelabra. This artery supplies adjacent parts of the frontal and parietal lobes.

After turning posteriorly in the sylvian fissure, the middle cerebral artery terminates by dividing into three branches: (a) the posterior parietal artery, (b) the angular artery, and (c) the posterior temporal artery (Fig. 1*A* and *B*). These vessels course posteriorly deep in the sylvian fissure for 3 to 4 cm. and then reach the sur-

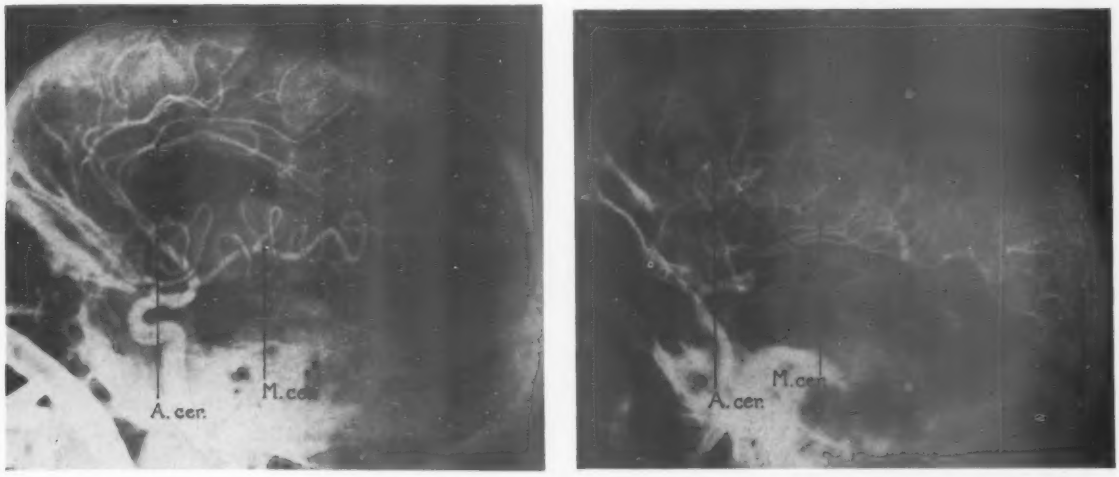

Fig. 25 and 26. Lateral views of the normal carotid angiogram to illustrate variations in the branching of the middle cerebral artery (arterial filling). In Figure 25 there is air in the lateral ventricles and basal cisternae from a pneumoencephalogram. In Figure 26 the middle cerebral artery has an unusual appearance because the proximal portion is seen end-on and is difficult to see in this view. The abrupt turn superiorly in the middle cerebral artery actually occurs far laterally in the sylvian fissure and does not represent elevation of the proximal portion of the middle cerebral artery. The proximal portion of the ascending frontoparietal artery is tortuous and courses anterior to its usual position. (Retouched.)

face of the brain in the posterior parietal and posterior temporal regions. The most superior branch, the posterior parietal artery, supplies the posterior and lateral aspect of the parietal lobe; the middle branch, the angular artery, supplies that portion of the brain around the angular gyrus, whereas the most inferior branch, the posterior temporal artery, supplies the posterior and lateral portions of the temporal lobe.

(b) Anatomical Variations. As with the other intracranial arteries, there is variation in the size of the middle cerebral artery. Its main trunk has an average diameter of about 2 mm. Absence of the middle cerebral artery has not been reported in the literature.

The main variation in the ascending frontoparietal artery is in the size and distribution of its branches (Fig. 16, 17, 18, 19, 20 and 27). The terminal branches do not always have the "candelabra" appearance and sometimes one of them supplies the cortical area usually supplied by the posterior parietal artery.

There is only slight variation in the size of the three terminal branches of the middle cerebral artery but great variation exists in their manner of origin from this artery. The posterior parietal, angular, and posterior temporal arteries may arise as one, two or three separate trunks (Fig. 25, 26 and 27). All of these branches show marked tortuosity and frequently cross each other. The proximal portions of these branches sometimes have a slight superior convexity which is difficult to differentiate from

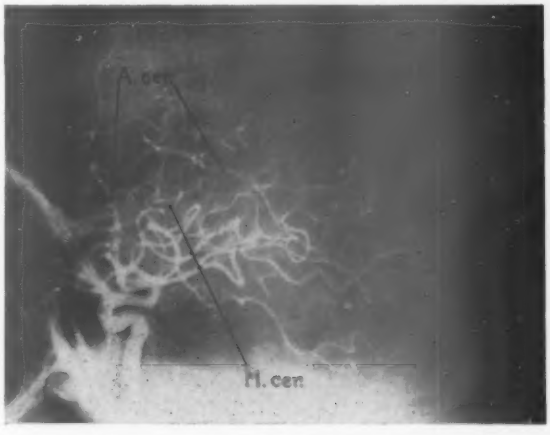

Fig. 27. Lateral view of the normal carotid angiogram (arterial filling). The anterior cerebral artery is tortuous. Note manner of branching of middle cerebral artery. (Retouched.)

minimal pathological displacement (Fig. 25). The tortuosity of these arteries is of help in ruling out the presence of displacement; when the displacement is due to tumor, the vessels are usually straightened. Fortunately, too, any mass large enough to displace one of these branches will usually displace one or both of the other branches and careful study of their relationship to one another will usually reveal the presence of a space-occupying mass if present. Stereoscopic views are essential in the study of these branches to demonstrate their spatial relationships. They may be grouped closely together or widely separated (Fig. 26 and 27) and there is great variation in their distal distribution. Sometimes the posterior parietal branch supplies that part of the brain supplied usually by the ascending frontoparietal artery (Fig. 17), and the posterior temporal artery sometimes supplies that portion of the brain usually supplied by the posterior cerebral artery (Fig. 26).

The middle cerebral arteries on the two sides of the brain are usually not symmetrical in their configuration or in their manner of branching.

(c) Physiological Variations. To our knowledge, absence of filling of the middle cerebral artery has not been reported in the literature. In our experience the only times during which the middle cerebral artery did not fill were those in which spasm of the internal carotid artery occurred. In these instances both the anterior and middle cerebral arteries failed to fill (Fig. 15*A* and *B*).

Bilateral filling of the middle cerebral arteries has been reported by several authors including Egas Moniz,[3] Engeset,[5] Löhr and Jacobi,[15] and Hemmingson.[11] In all cases, the phenomenon was due to reduced pressure in the contralateral carotid system caused either by manual compression of the opposite common carotid artery, by an arteriovenous fistula, or by a brain tumor. In our series. bilateral filling (Fig. 28) occurred in 2 essentially normal individuals, an incidence of 4 per cent. One patient had idiopathic epilepsy and the other had adhesive arachnoiditis of the optic nerve which was later demonstrated at operation. From these 2 instances, it appears that filling of the opposite middle cerebral artery may occur in normal cases. Although the cause of the filling is not entirely evident, it is conceivable that the increased pressure following the injection of the contrast medium was sufficient to force the material into the opposite middle cerebral artery through a large anterior communicating artery. This theory is supported to some extent by the fact that bilateral filling did occur in all four injections of the same patient.

Anteroposterior Projection.

(a) Roentgen Anatomy. The proximal portion of the middle cerebral artery extends laterally from the bifurcation of the internal carotid artery and is clearly visualized in this projection (Fig. 1*A*, 11*B*, 12*B*, 13*B*, 14*B*). Our observations of normal cerebral angiograms indicate that this portion of the middle cerebral artery is never elevated and that superior displacement is pathognomonic of a space-occupying mass in the temporal lobe. With a "double" type of carotid siphon the middle cerebral artery appears depressed below the level of the bifurcation, but this appearance is due to projection (Fig. 12*B*). The middle cerebral artery normally is at the same level as the bifurcation or at the most a few millimeters below it.

The ascending frontoparietal artery originates from the middle cerebral artery just before the latter turns posteriorly and branches into its terminal divisions (Fig. 2*A* and *B*, 13*B*). The ascending frontoparietal artery and its branches lie slightly medial to the terminal branches of the middle cerebral artery and are clearly seen in the anteroposterior view.

The middle cerebral artery divides into its terminal branches as it turns posteriorly in the sylvian fissure and at this point it lies about 2 cm. beneath the inner table of the skull. The terminal branches

are difficult to distinguish from one another because of superimposition; as they approach the surface of the brain they give rise to a fine network of vessels which lie adjacent to the inner table of the skull.

(b) Anatomical Variations. Variations in the size and position of the middle cerebral artery and its branches are best seen in the lateral projection. Elevation of the middle cerebral artery has not occurred in our series of normal cases.

(c) Physiological Variations. Absence of filling and bilateral filling of the middle cerebral arteries have already been discussed. Bilateral filling of the middle cerebral arteries is well demonstrated in this projection (Fig. 28).

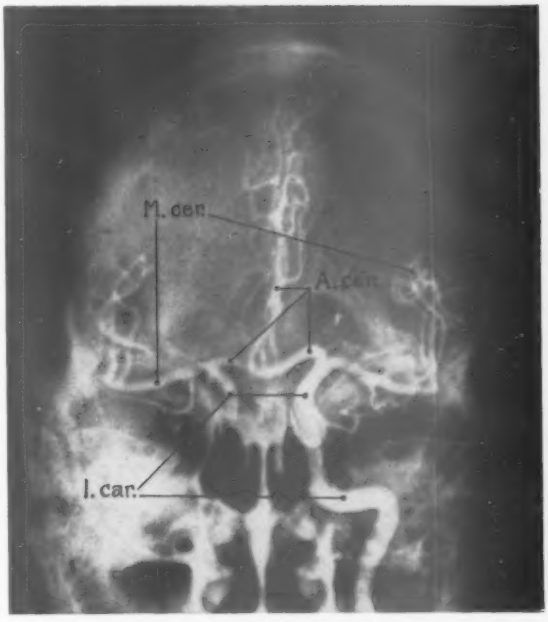

Fig. 28. Anteroposterior view of normal carotid angiogram (arterial filling). The film shows filling of both carotid systems with unilateral injection. There is slight reflux into the contralateral internal carotid artery. (Retouched.)

VERTEBRAL ARTERIES.

Lateral Projection.

(a) Roentgen Anatomy. The left and right vertebral arteries arise from the subclavian arteries, course superiorly in the neck and enter the skull through the foramen magnum. Thereafter they unite on the anterior surface of the lower border of the pons to form the single basilar artery. Each vertebral artery gives rise to lateral branches, known as the posterior spinal arteries, and a medial branch, called the anterior spinal artery. These vessels are difficult to see with vertebral angiography. The vertebral artery also gives rise to a larger branch, the posterior inferior cerebellar artery which courses laterally and posteriorly around the medulla oblongata and supplies the inferior and lateral surfaces of the cerebellum. None of these branches is well seen in vertebral angiography in our limited experience.

(b) Anatomical and Physiological Variations. Our own experience with vertebral angiography has yielded few significant variations in these vessels. Studies of autopsied cases in which one vertebral artery did not join the basilar artery have been reported.

Anteroposterior Projection.

(a) Roentgen Anatomy. The vertebral artery is easily identified in this projection but its branches are difficult to see (Fig. 5).

BASILAR ARTERY AND ITS BRANCHES.

Lateral Projection.

(a) Roentgen Anatomy. From its origin at the union of the vertebral arteries, the basilar artery (Fig. 3) courses superiorly and lies anteriorly to the pons and posteriorly to the dorsum sellae. It extends upward into the interpeduncular fossa, where it occupies a position 2 to 3 mm. posterior to the posterior clinoid processes and ends by bifurcating into two divisional branches The basilar artery gives off the paired anteroinferior cerebellar arteries, which pass posteriorly around the pons to supply the inferior surface of the cerebellum, and the paired superior cerebellar arteries which pass around the pons to supply the anterior surface of cerebellum. Both pairs of arteries are visualized in vertebral angiography (Fig. 3), although they are sometimes difficult to trace, not only because the vessels

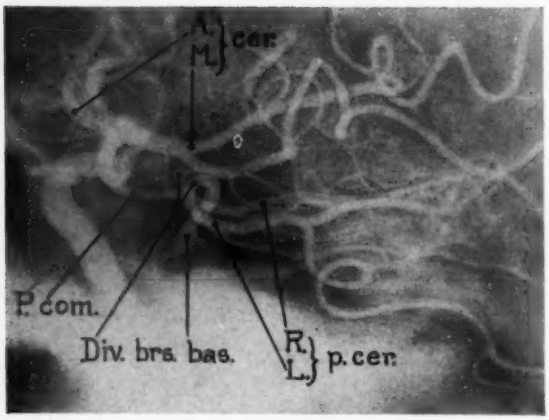

Fig. 29. Lateral view of the normal carotid angiogram (arterial filling). The posterior communicating artery fills and there is filling of both divisional branches of the basilar artery and both posterior cerebral arteries. There may be slight filling of the basilar artery. (Retouched.)

are often superimposed on each other but also because the superimposed bony structures of the skull limit the clarity of reproduction.

The paired divisional branches of the basilar artery are superimposed in the lateral projection (Fig. 3 and 29). Each divisional branch curves laterally to join with the posterior communicating artery of that side to form the posterior cerebral artery. Some anatomists use the term "proximal portion of the posterior cerebral artery" rather than "divisional branch of the basilar artery" to describe this vessel; either term seems acceptable.

(b) Anatomical Variations. Slight variations in the size of the basilar artery have been reported by Godinov.[9] Its usual diameter is about 3 mm. Absence of the basilar artery has not been reported in the literature nor is there mention of an abnormal position as seen in the lateral projection.

The cerebellar arteries are visualized at vertebral angiography, but our experience in this field is too limited to cite the variations that occur. No mention of a significant variation could be found in the literature, however. Vertebral angiography is discussed more completely in a recent article by Sugar, Holden and Powell.[22]

Saphir[20] and Sanchez-Perez[19] have indicated that the divisional branches of the basilar artery may be very small. Usually, however, they are the same size as the posterior cerebral artery. Absence of the divisional branch is not mentioned in the literature.

(c) Physiological Variations. The basilar artery always fills during vertebral angiography. The question as to whether or not the basilar artery ever fills in the normal case during carotid angiography is still not settled. Filling of the basilar artery by carotid angiography must be rather rare as the only report of this type of filling is by Egas Moniz[3] who reported its occurrence in 5 patients. A detailed case history of these patients was not given, but apparently they were not moribund. In 1 of the 5 cases there was no filling of either the anterior or middle cerebral artery but Egas Moniz did not comment on this. Egas Moniz believed that the basilar filling was due to the retrograde flow of the contrast medium down the carotid system into the vertebral artery and then into the basilar artery. That this is not the true explanation is suggested by Egas Moniz's roentgenographic illustration which shows no filling of the vertebral artery. It appears that a more likely explanation of the phenomenon is the retrograde filling of the basilar artery from the posterior communicating artery through changes in normal pressure relationships. Suggestive filling of the basilar artery was noted in one of our normal cases in which there was good filling of the posterior communicating and posterior cerebral arteries on the same side (Fig. 29).

Anteroposterior Projection.

(a) Roentgen Anatomy. The basilar artery is easily visualized in this projection (Fig. 5). From the union of the vertebral arteries, the basilar artery courses superiorly in the midline. Its branches extend laterally and are fairly symmetrical in distribution and size. Its terminal bifurcation into the two divisional arteries is clearly

seen and presents a T-shaped appearance. Each divisional branch extends almost directly laterally for a few millimeters and then turns posteriorly to join the posterior communicating artery of the same side to form the posterior cerebral artery.

(b) Anatomical Variations. There is very little information in the literature about anatomical variations of the basilar artery and its branches in this projection. In our own limited experience, the basilar artery often has a somewhat tortuous course (Fig. 5) and often lies some distance from the midline. The divisional branches have always been symmetrical in position and size.

POSTERIOR CEREBRAL ARTERY.

Lateral Projection.

(a) Roentgen Anatomy. The posterior cerebral artery is formed by the union of the posterior communicating artery and the divisional branch of the basilar artery about 2 cm. lateral to the bifurcation of the basilar artery. The posterior cerebral artery passes posteriorly to supply the inferior portions of the temporal and occipital lobes of the cerebrum (Fig. 3 and 4). It usually divides into two main branches. A superior branch supplies the posterior and middle portions of the temporo-occipital lobe, and an inferior branch supplies the posterior and medial portions of the occipital lobe. Both of these branches run posteriorly and closely parallel the course of the posterior cerebral artery itself. The posterior cerebral artery and its branches constantly lie a short distance inferiorly to the posterior temporal branch of the middle cerebral artery. Small arteries supplying the posterior part of the thalamus arise from the posterior cerebral artery and can be identified on the angiogram. These arteries curve superiorly and anteriorly.

(b) Anatomical Variations. The posterior cerebral artery varies from 1 to 2 mm. in diameter. Absence is not reported in the literature but Windle[23] mentions one case with two posterior cerebral arteries on one side, one of these arising from the basilar artery and the other from the internal carotid artery. The two posterior cerebral arteries were connected by anastomotic twigs. The posterior cerebral artery shows a fairly constant division into superior and inferior branches. This type of branching occurred in all of our cases, but there was variation in the distance between the origin of the posterior cerebral artery and the site of its branching (Fig. 3, 4 and 19).

(c) Physiological Variations. Filling of both posterior cerebral arteries has been consistently observed during vertebral angiography and frequently during carotid angiography (Fig. 4 and 19). In the latter instances, the phenomenon occurs by retrograde flow through the posterior communicating artery on the side of the carotid injection. In our series, the posterior communicating and the posterior cerebral arteries filled in 32 per cent of the cases and in 2 per cent of the cases there was filling of the posterior communicating artery without filling of the posterior cerebral artery. The incidence of filling of the posterior cerebral artery during carotid angiography is given in Table III.

TABLE III

Author	Filling of Posterior Cerebral Artery
Egas Moniz[3] (400 cases)	20.0%
Elvidge[4] (? cases)	14.0%
Fernandes[7] (25 cases)	32.0%
Green and Arena[10] (107 cases)	34.0%
Curry and Culbreth (50 normal cases)	32.0%

From the above statistics in Table III it can be seen that the posterior cerebral artery can be expected to fill from 20 to 30 per cent of the time during carotid angiography.

Filling of the posterior cerebral artery probably occurs more frequently when the posterior communicating artery is large and when the contrast material is injected rapidly. However, even when the posterior communicating artery is small, the pres-

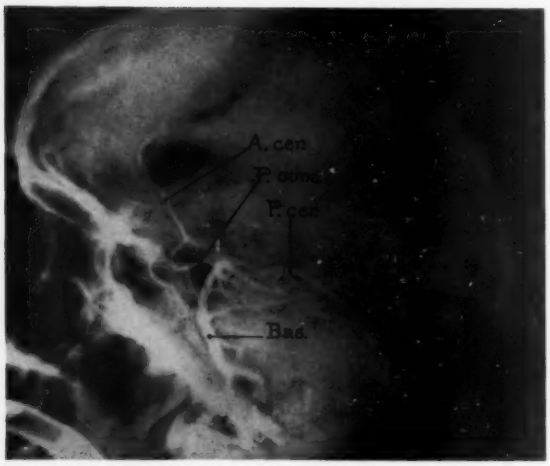

Fig. 30. Lateral view of the normal vertebral angiogram (arterial filling). This illustrates slight filling of the carotid system from flow through the posterior communicating artery. Air in ventricles is from a pneumoencephalogram. (Retouched.)

sure of the injection may be sufficient to fill the posterior cerebral artery (Fig. 19). It is not uncommon for the posterior communicating and posterior cerebral arteries to fill during one injection and not on subsequent injections.

In one of our cases of carotid angiography there was filling of the posterior communicating artery, both posterior cerebral arteries, and both divisional branches of the basilar artery (Fig. 29). The opposite posterior communicating artery did not fill but there was suggestive filling of the basilar artery. No mention of bilateral filling of the posterior cerebral arteries during carotid angiography has been found in the literature.

Anteroposterior Projection.

(a) Roentgen Anatomy. The posterior course of the posterior cerebral artery is easily followed either on the vertebral or carotid angiogram (Fig. 3 and 5). From its origin it runs slightly laterally and upward and then turns medially. Its branches are difficult to separate because of superimposition (Fig. 3). When both posterior cerebral arteries are filled, they are symmetrical in distribution.

(b) Anatomical Variations. The most common anatomical variation of this vessel is the site of its division into superior and inferior branches. This variation is best observed in the lateral projection. We have observed no significant variation in the course of the vessel in this projection. Absence of the posterior cerebral artery and variations in its size have been discussed.

(c) Physiological Variations. These variations are very apparent in this projection; they have been discussed in previous paragraphs, however, and therefore will not be reviewed here.

POSTERIOR COMMUNICATING ARTERY.

Lateral Projection

(a) Roentgen Anatomy. The two posterior communicating arteries are a pair of anastomotic vessels connecting the carotid and basilar systems and under certain conditions blood may flow through them from one system to the other (Fig. 4 and 30). Each posterior communicating artery arises from the supraclinoid portion of the internal carotid artery several millimeters proximal to the origin of the anterior choroidal artery (Fig. 1*A* and *B*, 6 and 10). It courses posteriorly and slightly inferiorly for about 1 to 2 cm. and then turns superiorly to join the posterior cerebral artery, forming a rather sharp angle with it.

(b) Anatomical Variations. The posterior communicating arteries present greater

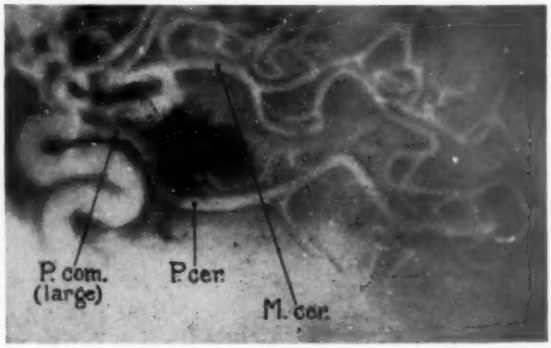

Fig. 31. Lateral view of normal carotid angiogram (arterial filling). The artery demonstrated here is either an anomalous posterior communicating artery or an anomalous vessel connecting the internal carotid artery with the posterior cerebral artery. (Retouched.)

anatomical variation in size than the vessels of any other portion of the circle of Willis (Fig. 4, 11*A*, 16, 18, 19). Some impression of this variation may be gained from Table IV where the observations of a number of workers are tabulated.

terior communicating artery which does not join the posterior cerebral artery at the usual angle but which is more or less in direct continuation with the course of the posterior cerebral artery (Fig. 31). This anomaly is difficult to differentiate in the

Table IV

Author	Absence of Posterior Communicating Artery		Diminution of Size of Posterior Communicating Artery One or Both Sides
	One side	Both sides	
Dandy[17] (review of 1,603 cases)	3%	0.3%	12%
Fetterman and Moran[6] (200 cases)	5%	0.5%	20%
Windle[23] (200 cases)	11%	1.5%	
Stopford[21] (111 cases)	6%		

From Table IV it will be seen that the posterior communicating artery is often small or absent. Although some authors maintain that the vessel is never entirely absent but is always represented by a small segment, it is for practical purposes absent at times. The size of the posterior communicating artery is of some importance because the relationship of its size to the divisional branch of the basilar artery determines whether the posterior cerebral artery receives its main blood supply from the carotid or vertebral systems. It also probably determines to some extent how often the posterior cerebral artery may be visualized during carotid angiography.

Sometimes the posterior communicating artery is larger than the divisional branch of the basilar artery and may be equal in size to the posterior cerebral artery. In Windle's[23] series of 200 autopsied cases, the posterior communicating artery was unusually large on one side in 10 per cent of the cases and on both sides in 2 per cent of the cases. Similar findings were recorded by Godinov[9] who found the artery unusually large on one side in 16 per cent and on both sides in 3 per cent of his autopsied cases. In our limited experience the most common anomaly of this vessel which may be confusing in angiographic interpretation is the occurrence of an unusually large posterior cerebral angiogram from a large anomalous communicating branch connecting the internal carotid artery with the posterior cerebral artery and paralleling the course of a small posterior communicating artery. Such an anomaly has been observed in autopsied cases and one of our normal cerebral angiograms showed a large artery in the position of the posterior communicating artery, which may or may not represent such an anomaly (Fig. 31).

(c) Physiological Variations. The posterior communicating artery may or may not fill during carotid or vertebral angiography. The incidence of this finding during carotid angiography has been discussed previously under the posterior cerebral artery. It not infrequently fills during vertebral angiography and is often associated with slight filling of the anterior and middle cerebral arteries (Fig. 30). Bilateral filling of the posterior communicating artery has not been reported in the literature and has not been observed by us.

Anteroposterior Projection.

(a) Roentgen Anatomy. The posterior communicating artery can often be identified in this projection but it is usually not well demonstrated since it is partially superimposed on the internal carotid artery (Fig. 11*B*, 13*B*).

EXTERNAL CAROTID ARTERY.

Lateral Projection.

Three branches of the external carotid artery are of angiographic interest. These are the middle meningeal artery, which divides into anterior and posterior branches and supplies the dura mater, and the superficial temporal and occipital arteries which supply the scalp (Fig. 9).

These arteries present only slight variation in size and only minor variations in their courses. Because of their position and configuration as seen in the lateral projection and because they are not intracerebral they can be easily distinguished from the branches of the internal carotid artery by stereoscopy. Identification of these branches is important to avoid confusion with cerebral vessels.

No physiological variations have been reported in the literature. In our series the branches of the external carotid artery filled in only 44 per cent of the cases. This was undoubtedly due to the fact that the cannula was more often in the internal carotid artery than in the common carotid artery. Many authors reported that the branches of the external carotid artery fill about one second later than those of the internal carotid artery, but in our cases there has usually been simultaneous filling of both.

Anteroposterior Projection.

This view is of little value in the study of the branches of the external carotid artery. The middle meningeal artery is very difficult to identify. The superficial temporal artery can be seen in the scalp superficial to the skull and the occipital artery is superimposed on the occipital bone.

B. Capillary System

The individual capillaries cannot of course be identified on the cerebral angiogram. Capillary filling produces a slight diffuse opacification of the brain. No significant abnormality has been observed.

C. Venous System

SUPERFICIAL CEREBRAL VEINS.

Lateral Projection.

(a) Roentgen Anatomy. The superficial cerebral veins drain the outer surface of the cerebrum and flow into the superior longitudinal and transverse sinuses (Fig. 7*A* and *B*). The principal vein in the parietal region drains into the superior longitudinal sinus and is known as the vein of Trolard. The largest vein in the posterior temporal and occipital region drains into the transverse sinus and is called the vein of Labbé. A third vein, the middle cerebral, is much smaller than the first two and lies more anteriorly. It drains the insular and opercular regions and anastomoses with the cavernous sinus as well as the superficial cerebral veins.

(b) Anatomical Variations. Marked variation exists in the size, number and distribution of the superficial cerebral veins. This is of some importance in cerebral angiography since these veins are sometimes displaced by space-occupying masses.

(c) Physiological Variations. None has been reported in the literature.

Anteroposterior Projection.

(a) Roentgen Anatomy. The superficial cerebral veins are easily seen in the anteroposterior view as they course medially to enter the superior longitudinal sinus (Fig. 8). When the veins of both cerebral hemispheres are filled, asymmetrical distributions of the veins are well demonstrated.

DEEP CEREBRAL VEINS.

Lateral Projection.

(a) Roentgen Anatomy. The deep cerebral veins consist of the paired internal cerebral veins, the paired basal veins of Rosenthal and the great cerebral vein of Galen (Fig. 7 *A* and *B*). Each internal cerebral vein begins at the interventricular foramen where it is formed by the fusion of the vein of the septum pellucidum and the terminal vein. As the terminal vein joins

the vein of the septum pellucidum, it makes a sharp turn, convex anteriorly, that is an extremely helpful landmark in locating the origin of the internal cerebral vein. The internal cerebral vein then courses posteriorly and inferiorly for several centimeters and joins its partner from the opposite side to form the vein of Galen. The fusion of the internal cerebral veins to form the single vein of Galen occurs just posteriorly to the pineal gland. The vein of Galen courses posteriorly and superiorly around the splenium of the corpus callosum and empties into the straight sinus at the latter's junction with the inferior longitudinal sinus.

The paired basilar veins of Rosenthal, which drain the insular and opercular regions course posteriorly around the cerebral peduncles to empty into the vein of Galen. Similar to the internal cerebral vein, there is only ipsolateral filling of the veins of Rosenthal during carotid angiography.

(b) Anatomical Variations. There is surprisingly little variation in the size and position of the internal cerebral veins and the vein of Galen. The distance from the anterior convexity of the internal cerebral vein to the posterior clinoid processes ranges from 3.0 to 4.0 cm. Although there is marked variation in the size of the basilar veins of Rosenthal, there is little variation in their courses.

(c) Physiological Variations. The internal cerebral veins and the vein of Galen can always be identified in satisfactory carotid angiograms. The basilar vein of Rosenthal cannot always be seen. Bilateral venous filling does not occur unless there is also bilateral arterial filling.

Anteroposterior Projection.

(a) Roentgen Anatomy. The deep cerebral veins are difficult to identify in this projection (Fig. 8). This is chiefly due to superimposition of the dural sinuses and superficial cerebral veins. We have found the anteroposterior view to be of little value in the study of the deep cerebral veins.

DURAL SINUSES.

Lateral Projection.

(a) Roentgen Anatomy. The dural sinuses which may be readily identified on the cerebral angiogram are the superior longitudinal sinus, the inferior longitudinal sinus, the straight sinus, and the paired transverse sinuses (Fig. 7*A* and *B*). The cavernous sinus, petrous sinuses, and internal jugular vein are very difficult to identify with certainty. The positions of these sinuses differ from those given in anatomical descriptions only in that the straight sinus forms a somewhat more acute angle with the distal part of the superior longitudinal sinus than that shown in most textbooks. The transverse sinuses are usually superimposed in this view.

(b) Anatomical Variations. Very little variation exists either in the size or course of the dural sinuses. Since the straight sinus is sometimes displaced by brain tumors and since it indicates the position of the tentorium cerebelli, measurements were made to determine its normal position. The distance from the inner table of the skull in the region of the lambda to the junction of the vein of Galen and straight sinus ranged from 5.0 to 6.0 cm., the longer distance occurring in the scaphocephalic type of skull.

(c) Physiological Variations. No physiological variations were noted in our series of cases and none is reported in the literature.

Anteroposterior Projection.

(a) Roentgen Anatomy. Since the superior longitudinal sinus, inferior longitudinal sinus, and straight sinus all lie in the midline, they are superimposed in this projection and are difficult to distinguish (Fig. 8). The transverse sinuses can often be faintly seen.

DISCUSSION

In the foregoing paragraphs the normal angiographic anatomy of the cerebrovascular system has been discussed in con-

siderable detail. As in other vascular systems, the courses and distributions of the cerebral vessels present considerable variation. Since some of these variations follow patterns similar to those produced by pathological change, it is important that a thorough knowledge of the limits of normal cerebrovascular anatomy be established if serious errors are to be avoided in the interpretation of angiographic films.

Undoubtedly, many of our present concepts of normal and abnormal angiographic anatomy will be altered in the light of future investigations. However, it seems worth while to present those data which seem reliable at this time in the hope that they will serve as a guide for those interested in cerebral angiography.

There are several instances where normal anatomical or physiological variation may be confused with pathological change. For example, the intracranial portion of the internal carotid artery may present early changes from an intrasellar, suprasellar, or parasellar mass, but such changes may also be caused by a normal tortuosity of the artery. The anterior cerebral artery usually extends down the midline of the brain and shows a lateral shift when there is a brain tumor nearby; here again, large deviations from the midline are sometimes produced by no more than a normal tortuosity of the vessel. On the other hand, the middle cerebral artery is useful in localizing masses in the parietal and temporal lobes for we know that elevation of the proximal segment of this artery is always abnormal. Depression of the vessel, seen in the anteroposterior view, however, may not be of any significance, especially if the artery in the later view is not straightened.

Bilateral carotid angiography has shown that the two anterior cerebral arteries often do not follow the same course and that there is a similar variation in the position and manner of branching of the middle cerebral arteries. Comparison of the vessels on the two sides of the brain in cerebral angiography is therefore not as useful as the comparison of the two lateral ventricles of the brain when determining the presence or absence of pathology.

Marked variation in size of the components of the circle of Willis exists and is an important factor in determining blood flow and pressure relationships in the cerebral vessels. Marked narrowing of the posterior communicating artery is common and similar change can occur in the proximal segment of the anterior cerebral artery. In both cases knowledge of these variations is very useful in the interpretation of unusual types of vascular filling.

Two uncommon but important anatomical variations, which have been described in the literature on autopsied material, have been noted in our series of cases: a middle anterior cerebral artery and an anomalous vessel connecting the internal carotid artery with the posterior cerebral artery.

Physiological variations in the filling of the vessels is common due to marked differences in the size of the components of the circle of Willis and to altered pressure relationships produced by the force of the injection. Although there is usually ipsilateral filling of the cerebral vessels with carotid angiography, bilateral filling can occur under normal conditions as well as in disease. Absence of filling may occur and does not necessarily indicate pathological closure of a vessel. Repeated injections of the contrast medium may be necessary to differentiate physiological from pathological absence of filling.

Bilateral filling of the anterior cerebral arteries is common; bilateral filling of the middle cerebral arteries is uncommon. Absence of filling of the anterior cerebral artery during one injection is not rare and could conceivably occur during all injections without being pathological. Absence of filling of the middle cerebral artery with good filling of the anterior cerebral artery has never been described. Filling of the posterior communicating artery and posterior cerebral artery during carotid angiography is common but is rarely accompan-

ied by filling of the basilar artery. Similarly the carotid system may fill during vertebral angiography.

These then are some of the more important of the vascular variations which may be seen with cerebral angiography. It is hoped that this study may be of benefit to those who are confronted with problems in the interpretation of cerebral angiograms. As we have pointed out, normal variations frequently simulate changes produced by pathological processes and unless they are continually borne in mind mistakes in interpretation may easily be made.

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CONTRAST MYELOGRAPHY WITH EMULSIFIED PANTOPAQUE

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WHEN it becomes necessary to resort to contrast myelography in studying the patient suspected of having intraspinal pathology, the choice of media is rather limited.[4] Though various media have been proposed, all fall short of the ideal in some respect. The ideal contrast medium for intraspinal use should be (1) non-toxic, (2) of sufficient atomic weight to cast a clear-cut shadow, (3) non-irritating, (4) miscible with cerebrospinal fluid, and (5) readily eliminated.[1]

The types of media which have been given most consideration are four in number: (1) the oils, (2) the gases, (3) the colloidal suspensions, and (4) the aqueous solutions. The most commonly used of the oil type media are pantopaque and lipiodol. The gases commonly used in myelography are oxygen or air. The suspension type medium is represented by thorotrast (thorium dioxide sol) and diiodotyrosine-gelatin, while the solution type medium is represented by skiodan.

Of the various media mentioned here, pantopaque at the present time seems to be the most favorable for use in clinical myelography. This medium (ethyl-iodophenylundecylate) was developed by Strain, Warren and Plati[7,8] in 1942. It is clear oil with a slightly yellowish tinge and contains 30.5 per cent of iodine in organic combination. It has a density of 1.263 at 20 degrees centigrade. Its viscosity is relatively low, lipiodol being seventeen times as viscous as pantopaque at 37.5° C. The coefficient of viscosity of pantopaque is 0.217 at 37.5° C.[6] It is non-toxic and gives a sharp outline of the subarachnoid space because of its high degree of radiopacity.

Though varying degrees of meningeal irritation (inflammatory and/or proliferating type) have been reported following the use of this medium, the possibility of reaction to this foreign substance is minimized by removing a greater portion of it from the subarachnoid space by aspiration under roentgenoscopic control.[5,9] Its low viscosity and surface tension not only facilitate its removal but likewise make possible the delineation of the finer detail in the subarachnoid space. In this consideration, it is definitely superior to lipiodol. Though the pantopaque films are satisfactory in many respects, they fail to outline the spinal subarachnoid space with the same degree of clarity as did the formerly used thorotrast. This medium is of the colloidal suspension type, the colloid being thorium dioxide in a protective colloid, i.e., dextrin preparation. Since the colloidal particles of thorium dioxide were in suspension and were distributed throughout the cerebrospinal fluid in the area under study, it was possible to examine the finer detail of the subarachnoid space with a higher degree of accuracy than was possible with other media. Because of its potential radioactivity, the material was removed by forced spinal drainage upon completion of the roentgen examination.[2,3]

Unfortunately, after five years of extensive clinical use, the abrupt appearance of rather severe meningeal reactions to this agent precluded its further use until an adequate explanation for such reactions could be found. No effects which could be attributed to radioactivity were noted in any of the patients in whom this media had been used over the previous nine years, and had been rechecked.

Since the smallness of the thorium dioxide particle seemed to be a factor in delineation of the finer subarachnoid detail, it occurred to a colleague* that possibly emulsification of pantopaque into similar small particles would be productive of the same result.

* Dr. W. J. Gardner.

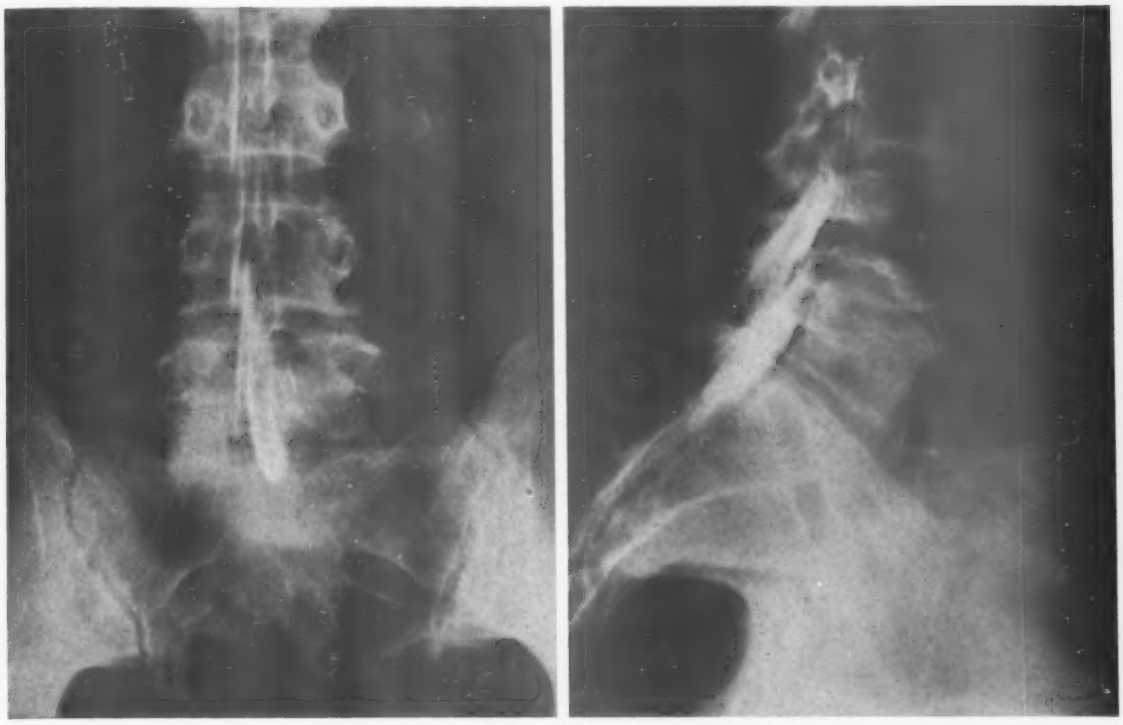

Fig. 1. Myelogram using 1.0 cc. pantopaque emulsified in 9.0 cc. cerebrospinal fluid. Protrusion of intervertebral disc confirmed at operation and located between the fourth and fifth lumbar vertebrae on observer's right.

Various attempts at emulsifying the pantopaque were made, though none was believed to be adequate. The method finally used consisted of shaking a given amount of pantopaque (in enough spinal fluid to produce a total of 10 cc. volume) for three minutes. At the end of this three minute period, the emulsion was injected into the lumbar area and the subsequent films made. After the roentgenograms had been made, as much of the cerebrospinal fluid-oil globule material was removed by aspiration as possible. Because of the fact that it presented only a shadowy outline under the fluoroscope, the removal of this material was not complete. The amounts used varied from 0.8 cc. to 3.0 cc. of pantopaque. In the films presented here (Fig. 1 and 2), it is apparent that there is considerably less masking when the emulsion form of pantopaque is used than there is if a solid mass is injected. Where the smaller amount of pantopaque has been used, it is somewhat surprising to note how much of the lumbosacral space can be outlined.

In a series of patients where emulsified pantopaque was used as a contrast medium, it became apparent that there was a remarkable inconstancy in the behavior of this medium. It would frequently settle out into a solid mass losing all of its emulsion characteristics. Likewise, a smaller amount, i.e., 1.0 cc., would often give a greater and more accurate outline of the spinal subarachnoid space than would 2.0 cc. It is believed that this inconstancy of behavior may be related to the crudity of the emulsion.

If a uniform pantopaque-in-cerebrospinal fluid emulsion or a pantopaque-in-saline emulsion could be made without alterating the character of the medium, this type of myelography might bear further investigation. While it shows some promise, an effort must be made to stabilize the emulsion before this technique can be properly evaluated.

CONCLUSIONS

(1) The use of emulsified pantopaque in clinical myelography is presented here.

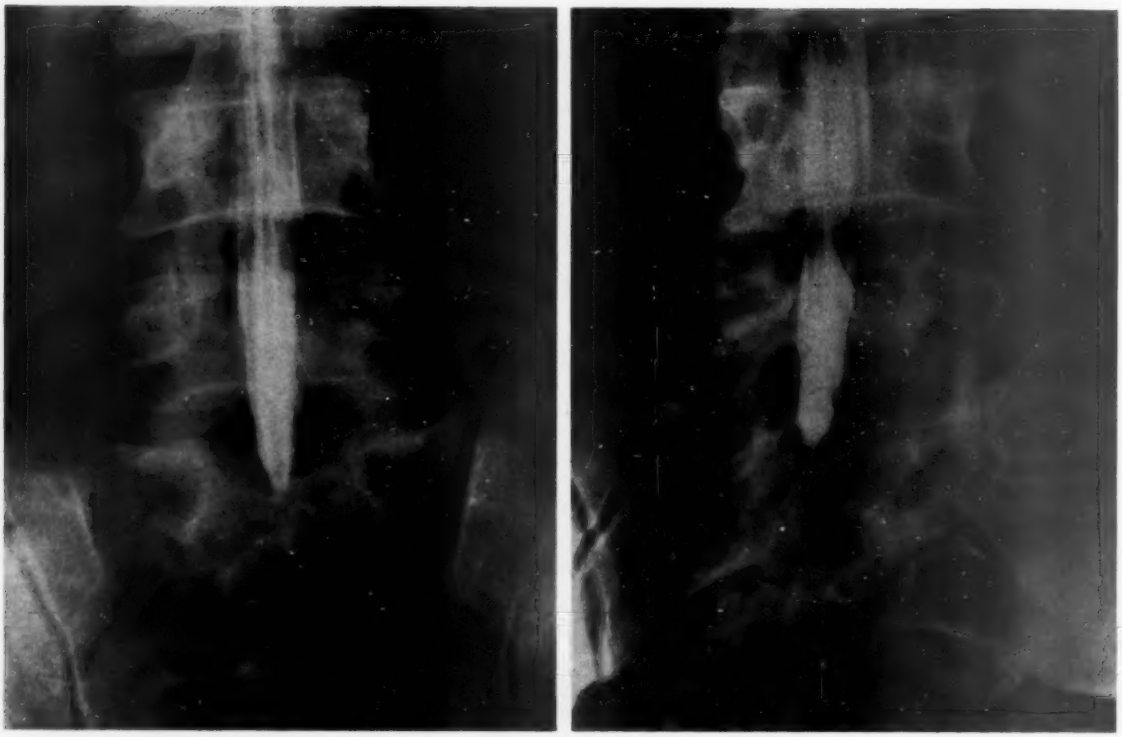

Fig. 2. Myelogram showing disc protrusion at the fourth and fifth lumbar vertebrae on observer's right, using 3.0 cc. pantopaque emulsified in 7.0 cc. of cerebrospinal fluid. Lesion confirmed at operation.

(2) The results were generally unsatisfactory when compared to other contrast media, probably because of the instability of the emulsion. If a uniform stable pantopaque emulsion can be made, further effort along this line may be justified.

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ADDENDUM

The irritating effect of pantopaque emulsions on the nervous system has been studied recently by Rudolph Jaeger, *Arch. Neurol. & Psychiat.*, Nov., 1950, *64*, 715–719.

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INTERVERTEBRAL JOINT SUBLUXATION, BONY IMPINGEMENT AND FORAMEN ENCROACHMENT WITH NERVE ROOT CHANGES

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SINCE each peripheral nerve must pass through an intervertebral foramen, any possible pathology involving this "crossroads" between the nervous system and its skeletal support must be considered in evaluating the symptoms of nerve root pressure.

FIG. 1. Oblique section, normal lumbosacral, 3rd disc more lateral, 5th disc nearer midline. There is ample cushion space about the nerve root. The foramen is bounded posteriorly by the ligamentum flavum which in part forms the anterior capsule of the apophyseal articulation. In addition to the nerve the foramen contains blood vessels, fatty and areolar tissue.

ANATOMY OF THE FORAMEN

In front, the foramen is bounded by the vertebral bodies and the posterolateral surface of the disc between them, while above and below are the pedicles. Posteriorly, occur the superior and inferior articular processes united by the lateral prolongation of the ligamentum flavum which at this point constitutes the anterior fibers of the capsule of the posterior articulation (Fig. 1).

Study of the section of a normal foramen reveals the oval nerve or its ganglion oc-

FIG. 2. A group of normal lumbar foramina. Intervertebral disc at left in each case. Note the relative sizes of the foramen opening and the nerve roots passing through it. There is an ample reserve safety cushion space about the nerve, containing blood vessels, areolar and fatty tissue. In specimen at the lower left there is some hyperplasia of the ligamentum flavum.

Fig. 3. (*A*) Left side of cervical spine of a cadaver showing congenital fusion of C_3 and C_4, also of D_1 and D_2. (*B*) 45° roentgenogram of right side of this same cadaver. Foramina C_3 and D_1 are at levels of non-segmentation. These openings are smaller than normal, smooth in outline and round or oval in shape. (*C*) Sections of these foramina after the roentgenogram reveal: C_4, C_7 and D_2 normal, C_5 and C_6 bony constriction of these openings (the saw cut passed through the bottom of C_5). Although C_3 is a non-segmented foramen, it is ample and the nerve root does not completely fill it. Non-segmented foramen D_1, however, is smaller and the nerve root occupies most of the opening. In the absence of movement no cushion space is necessary.

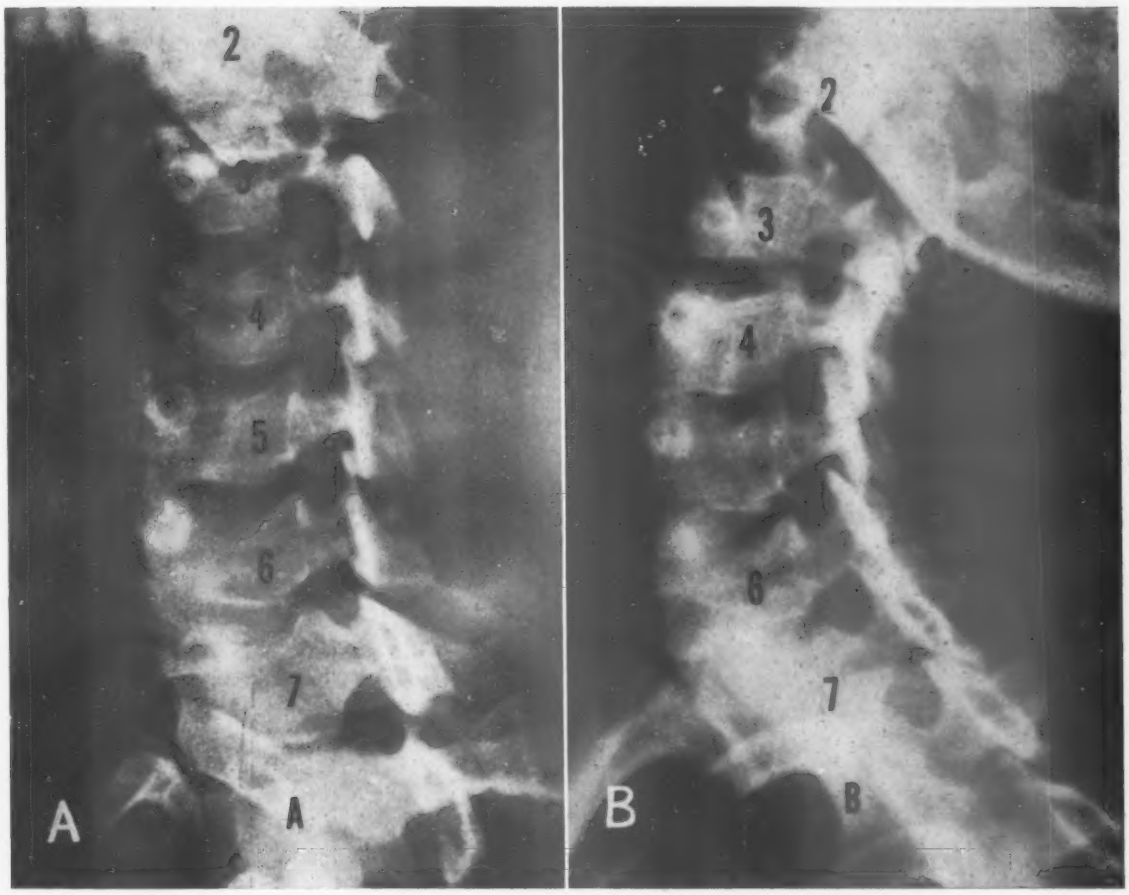


Fig. 4. (*A*) Normal cervical spine upright, note size of foramina. (*B*) Same patient, in dorsal extension, showing decrease in size of foramina as a result of this movement.

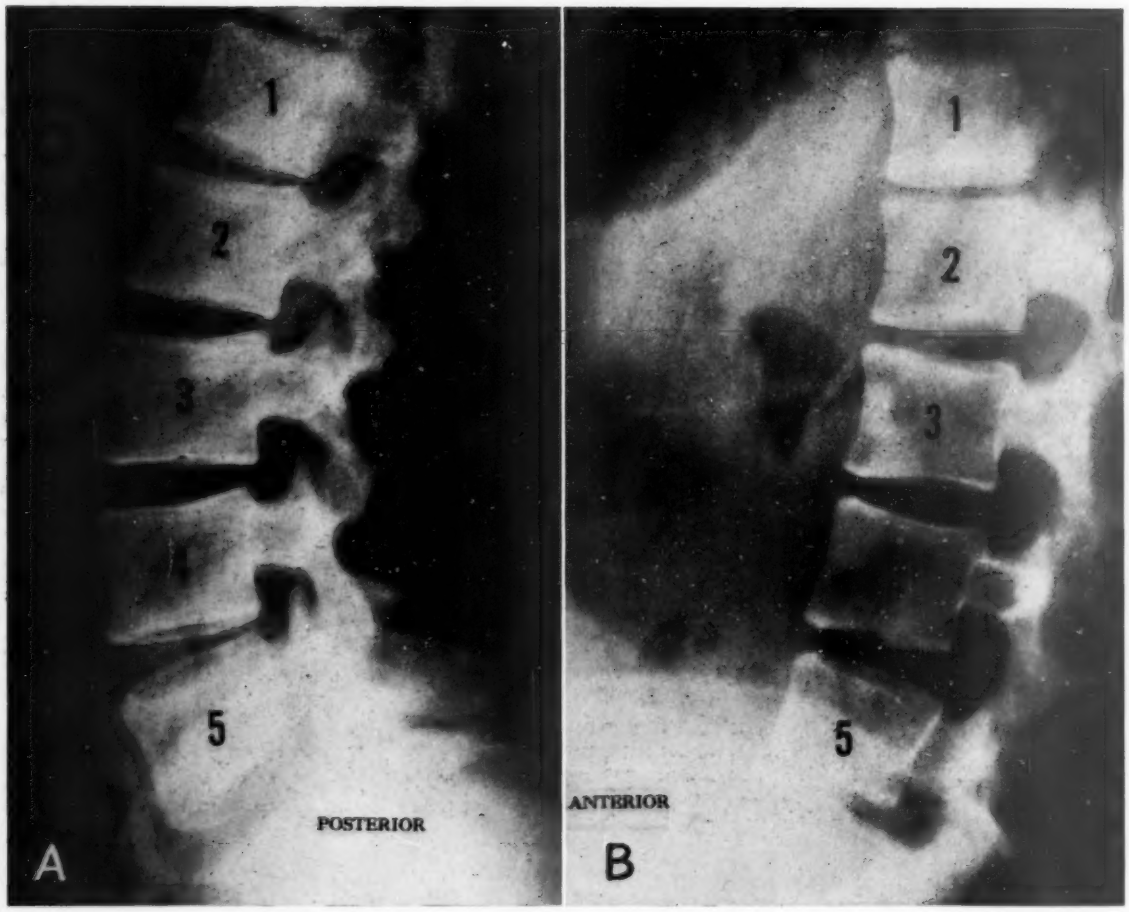


Fig. 5. (*A*) Posterior extension of lumbar spine. Note constriction of foramina. (*B*) Anterior flexion. Diameter of openings increased by this movement.

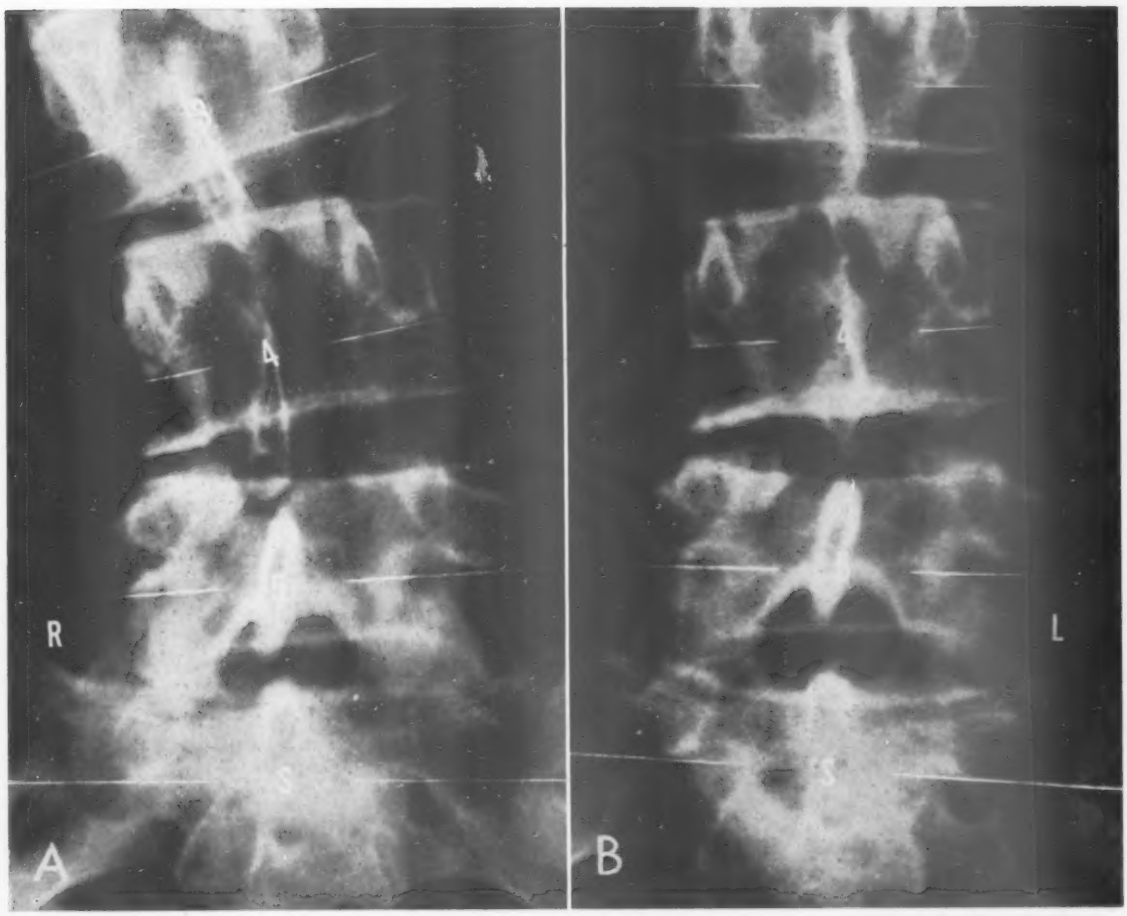


Fig. 6. Right and left lateral flexion. Female, aged eighteen, while lifting a heavy weight, felt sudden pain down the left leg. She maintains forward stooped position with list of spine away from painful side. Diagnosis confirmed by operation: herniated disc left side, 4th lumbar foramen. Films made in standing position. Lines indicate corresponding plane of the vertebral body in each of the photographs. (*A*) shows normal flexion toward right side. Note that the foramen (interpeduncular distance) becomes larger on the side away from which the bending occurs and smaller on the concave side. In attempting to stand upright, the patient held the spine with a list away from the left or painful side keeping the 4th foramen as large as possible. (*B*) Attempted left lateral flexion, lower lumbar spine held rigid. L_4 disc wedge shaped, indicating attempt to hold the corresponding foramen as large as possible. It must be remarked that lateral flexion studies of a patient, with localized lumbar injury only, may show this restricted movement but without the accompanying clinical picture of nerve root pressure.

cupying only from one-sixth to one-fourth of the opening. Surrounding this are blood vessels, lymphatics, sympathetic nerve fibers, fibrous and fatty tissue (Fig. 2).

This reserve space (three-fourths of the area within the foramen about the nerve root) consitutes a safety cushion allowing

Fig. 7. (Pedicles accentuated) Normal 45° lumbosacral. The interpeduncular distances shown by arrows indicate the cephalocaudad diameters of the foramina. At the 5th foramen this is measured between the cortex of the ala of the sacrum and the cortex of the 5th lumbar pedicle. The 5th posterior articulation occupies its normal position slightly anterior to the plane of the 4th.

the normal foramen constriction, incidental to all spinal movements, to take place without root compression.

In those spinal foramina where no such movement occurs, notably congenital nonsegmentation, no such cushion space is necessary and the foramen is likely to be smaller and round or oval, and the nerve may fit the foramen more closely (Fig. 3).

SPINAL MOVEMENTS

In the cervical region the extremes of lateral flexion, dorsal extension or rotation may normally decrease the size of the foramen by as much as one-third on the side toward which the movement takes place (Fig. 4).

In the lumbar region, lateral bending normally causes a similar physiological encroachment with a corresponding enlargement of the opening on the side away from which the movement occurs. Anterior flexion results in a substantial enlargement of all lumbar foramina while dorsal ex-extension produces the opposite effect (Fig. 5).

These normal physiological movements are to be considered in evaluating or eliciting the symptoms of nerve root pressure (Fig. 6).

Contralateral list of the lumbar spine away from the side of a sciatica indicates a protective attempt to enlarge the foramen of exit of a painful nerve root. In one patient studied, this contralateral list was lost when the foramina became enlarged by anterior flexion. As the patient bent forward his body swung towards the midline, i.e., the painful side, until the spine was in a symmetrical position. As he straightened up the reverse movement occurred and he gradually reassumed his contralateral list away from the painful side upon again reaching the vertical position.

Homolateral list toward the side of a sciatica indicates an attempt to lessen tension upon the involved nerve. A patient may show a combination of homolateral list and forward flexion, thereby relaxing the nerve tension and at the same time enlarging the foramen of exit.

Homolateral and contralateral scoliosis may alternate in the same patient.

A patient with lumbar foramen encroachment may obtain relief from pain by maintaining a position of forward flexion

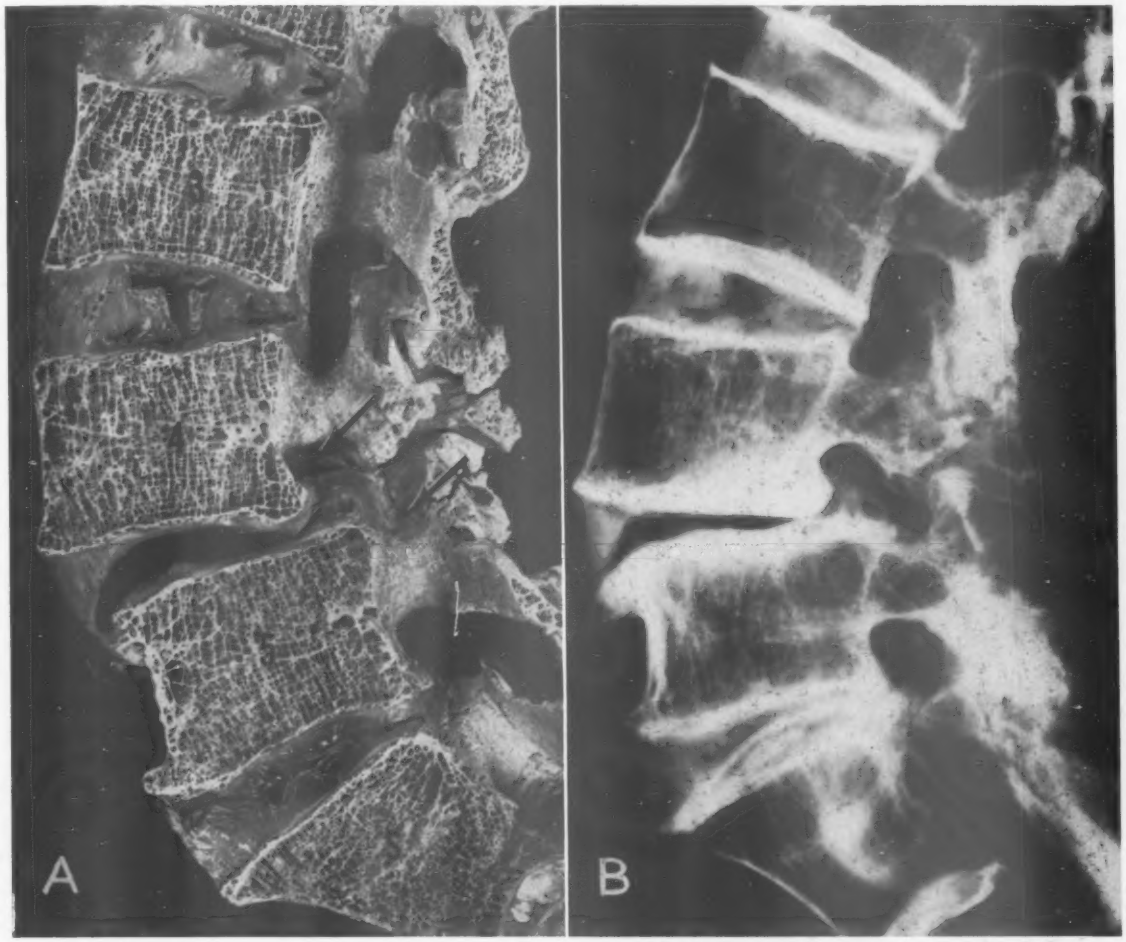


Fig. 8. (*A*) Sagittal section of cadaver specimen. False joint in 4th neural arch with spondylolisthesis of 4th lumbar forward on the 5th. Bulging of disc substance into foramen. Nerve still in situ compressed into small thin structure (between arrows). (*B*) Roentgenogram of this specimen showing spondylolisthesis and 4th foramen constriction; other foramina normal.

but the pain will be aggravated upon dorsal extension. This was marked in the patient reported in Figure 6 whose spine remained fixed in ventral flexion, even during painful heroic attempts at backward bending. Pain in the arm and shoulder from brachial root pressure may be aggravated by dorsal extension of the neck or by rotation or flexion toward the affected side. These patients hold the cervical spine straight, thereby eliminating its normal anterior curve.

TECHNIQUE

In the cervical region, the foramina open for the most part forward and laterally 45° and downward about 10°, the second and seventh being directed somewhat more laterally.

The best visualization has been attained by having the patient sit very straight upright, his back toward the tube. The sagittal plane of the skull and the transverse plane of the body are each placed 45° to the plane of the film by sighting downward from above across a 45° triangle cut from thin plywood. The occlusal plane of the teeth should be horizontal, with a block between cheek and cassette holder, and the upper edge of the 8 by 10 inch film at the level of the ear. The central ray is directed downward 10° and centered on

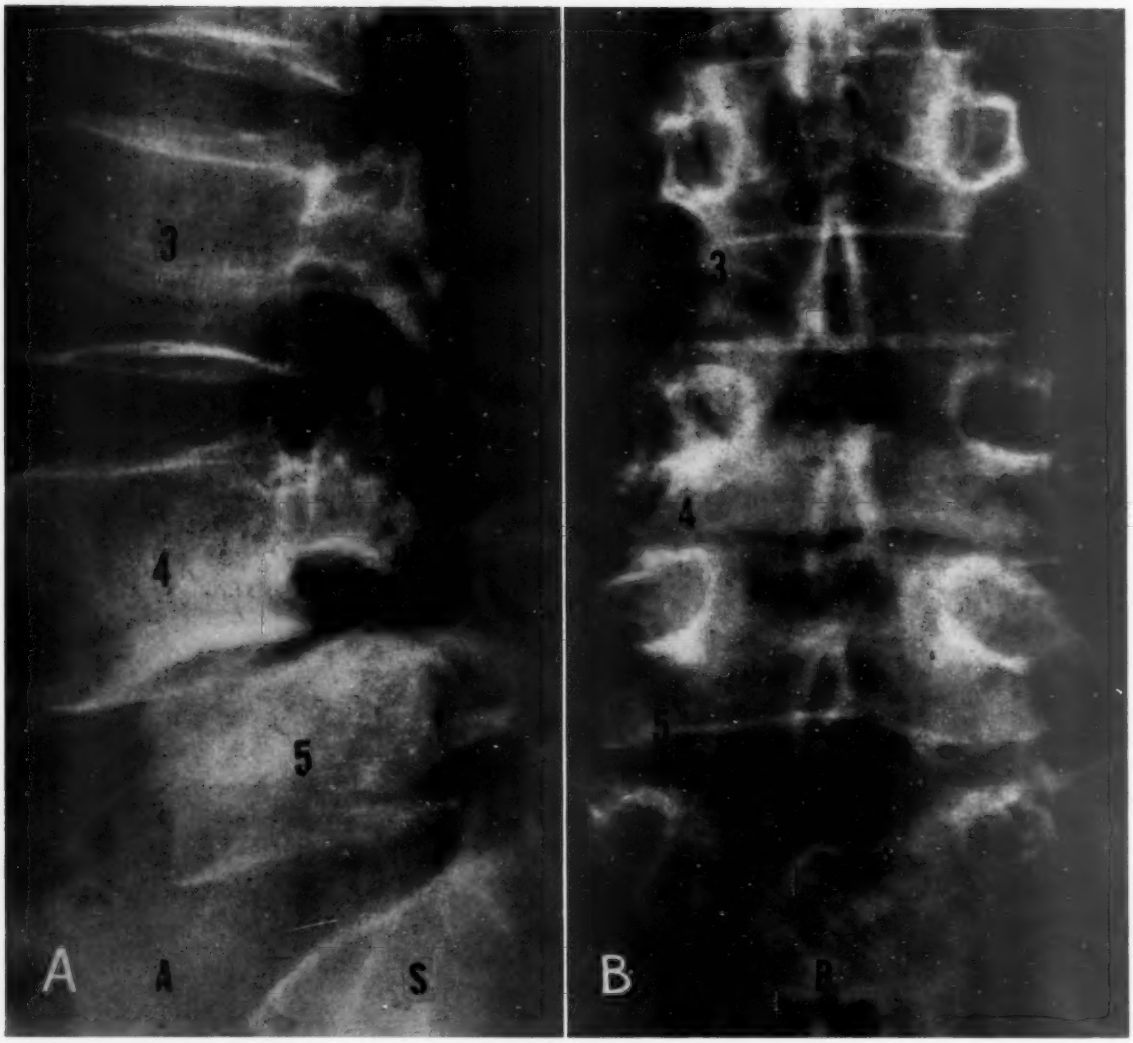


Fig. 9. Female, aged sixty-two. Pain in legs since falling from horse at age of sixteen. (*A*) Break in 4th neural arch. Spondylolisthesis L_4 forward on L_5. Compare this roentgenogram with Figure 8*B*. (*B*) Anteroposterior view (pedicles retouched) 4th lumbar foramen constricted but 3rd and 5th interpeduncular spaces normal.

Fig. 10. Male, aged sixty-three. Pain in back and down right leg. Achilles reflex diminished. Short lumbar region with limited movement. Second degree spondylolisthesis L_5 forward and downward on the sacrum of long standing with distortion of 5th foramina. Reverse spondylolisthesis of L_1 and L_2 backward upon the underlying bodies with encroachment of the corresponding foramina.

Fig. 11. Male, aged seventy. Pain in lower lumbar region. Thinning of 1st and 2nd lumbar discs. Because of the incline to the plane of the posterior articulation between L_2 and L_3 the second body was forced to subluxate backward (reverse spondylolisthesis) as the disc became thinned and the vertebral bodies came closer together. (Compare with L_2 in Fig. 10.) This decreases the anteroposterior diameter of the foramen. Also the 3rd superior articular process subluxates upward and forward causing additional foramen constriction. The first lumbar disc is also thinned but since no subluxation of the posterior articulation occurred, the foramen remained normal in size and shape and the patient developed a kyphosis at this level. There is also a reverse spondylolisthesis of L_3 backward on L_4, with a tipping of the vertebra so that the disc is much thicker anteriorly than posteriorly. As a result, a subluxation of the 4th superior articular process has occurred upward into the 3rd foramen, markedly encroaching upon that opening.

Fig. 12. Forty-five degree oblique section transverse to normal cervical foramina. In spite of disc degeneration with anterior spur formation in the mid cervical region, the intervertebral foramina have remained essentially normal in shape and size. There is a reserve safety cushion space about each nerve. Note intimate relationship between the nerve roots and the vertebral artery (arrows). Head of the first rib is seen opposite D_1.

Fig. 13. Forty-five degree oblique section transverse to constricted cervical foramina. Cadaver, aged eighty-five. Degeneration with thinning of the 4th, 5th and 6th discs. Encroachment of the corresponding foramina with loss of cushion space and some distortion of the 5th nerve (arrow). There is sclerosis of the surrounding bony tissue. (Compare with Fig. 12.)

Fig. 14. Two groups of sections of the intervertebral foramen removed from the cervical region, disc on the left side in each case. The group above shows normal foramina with ample cushion space surrounding the nerve roots. In the lower group all foramina are encroached upon by bony spurs from the disc or the posterior articulation. In one the nerve root has fallen out but this section shows well the bony spur projecting backward from the disc.

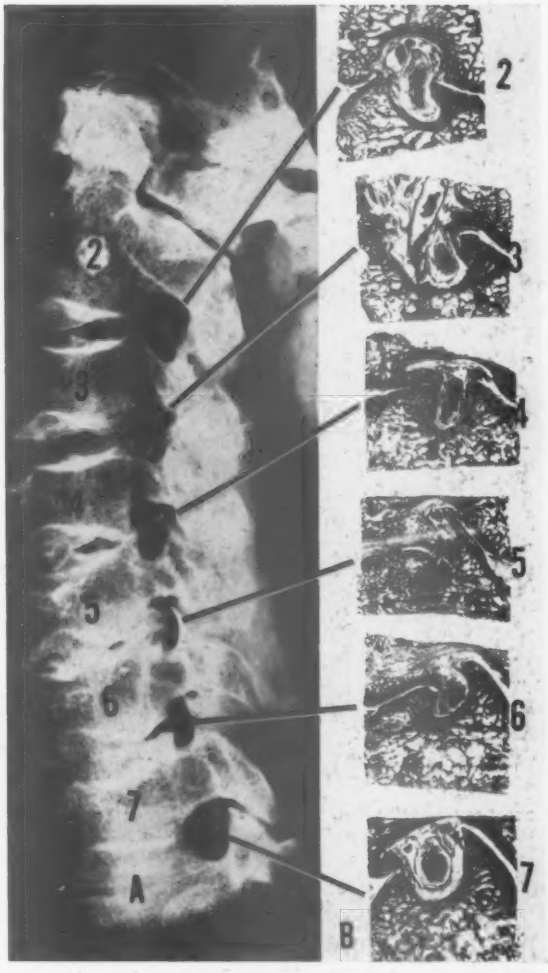


Fig. 15. (*A*) 45° roentgenogram of cervical spine from male cadaver, aged seventy-five. The 2nd, 3rd and 7th foramina are normal, the others show encroachment. (*B*) Sections cut from these foramina after the roentgenogram show the uppermost and the 7th roomy with plenty of cushion space about the sectioned nerve root. There are numerous blood vessels seen in the upper part of these two openings. The 3rd foramen has no bony encroachment but the vertebral artery lies closely adjacent to the anterior surface of the nerve. The 4th, 5th and 6th foramina exhibit marked bony encroachment and the nerve has losts its customary surrounding safety cushion space.

Fig. 16. Female, aged seventy-two. Pain in cervical region referred down left arm. Limitation of all neck movements. Muscle spasm. Tenderness to deep pressure left side of neck. Left oblique 45° film shows bony encroachment of the 3rd and 5th foramina, both from the disc in front and the posterior joint as well. (Compare with Fig. 15.)

the mid cervical region from a distance of 6 feet (Fig. 4*A*).

In the lumbar region, the foramina at each side of the spinal canal overlie each other in the lateral view. To separate them it is necessary to turn the patient slightly. To visualize the fifth lumbar foramen, the patient should be placed on the side to be studied but turned 10° toward the prone from the true lateral position. The central ray is angulated 10° toward the feet and centered just above and behind the iliac crest. Stereoscopic studies with transverse shift will show the fifth lumbar foramen en face through the lower most iliac bone.

A comparison of the cephalocaudad diameters of different foramina can be made from the anteroposterior view by noting the distance between the pedicles of adjacent vertebrae, although, of course, this gives no idea of the anteroposterior diameter of the openings (Fig. 9*B*). The 45° lumbar film (prone or supine) gives an excellent visualization of the posterior articular processes and the joint between them. Here the foramen is not seen en face but, as in the anteroposterior view, its size can be judged from the interpeduncular distance. For the fifth lumbar, this is measured from the cortex of the ala of the

Fig. 17. J. G. Male, aged seventy-four. Low backache and muscle spasm but no sciatica. Subluxation with impingement of 4th left articulation above and below (arrows) with erosion of the bony surfaces against which the impingement takes place. Pedicles retouched to indicate clearly the interpedunculate foramen openings, the 4th being slightly constricted on the left side.

sacrum upward to the undersurface of the pedicle of the fifth lumbar (Fig. 7).

INTERVERTEBRAL FORAMEN CONSTRICTION

Any abnormal constriction in the size of a movable intervertebral foramen if not actually causing nerve root pressure, nevertheless decreases the reserve safety cushion space surrounding that nerve and may predispose to pressure. The subsequent development of edema or hemorrhage in such a nerve will produce such pressure.

Trauma, either fracture of the vertebral body, fracture of its arch or dislocation of one vertebral body upon another, may cause encroachment or even obliteration of the foramen.

Somewhat related to dislocation are cases of spondylolisthesis. Some of these show foramen encroachment and some do not (Fig. 8 and 9).

Reverse spondylolisthesis is a very definite entity and produces foramen encroachment.[12] This results when the articular process from below becomes subluxated forward and upward into the foramen, a condition usually resulting from disc degeneration, or tipping of the vertebral body (Fig. 10 and 11).

Studies of the cadaver specimens indicate disc degeneration to be the most common cause of foramen encroachment.

As the degeneration and disc thinning occur the vertebral bodies approach more closely and a sclerosis of their plane surfaces develops. This type of bony reaction results from the irritation of pressure between two bone surfaces uncovered by articular cartilage and is greatest at the point of greatest pressure. Sclerosis is also noted in telescoping of the posterior articulation when impingement occurs between the tip of an articular process and the pedicle above or the lamina below. This degenerative or wearing out process commonly termed "osteoarthritis" is in no sense an inflammation of the joint and therefore may be more properly termed an arthrosis (Fig. 24*D*).

Fig. 18. Male, aged fifty-two. Low back pain and intermittent sciatica, ten years' duration. Degeneration of 4th disc with sclerosis and spur formation. Telescoping and subluxation of 4th and 5th posterior articulations with impingement (*X*) and foramen encroachment. Upper end of 5th superior articular process has become squared off. The articular surfaces of this joint are not parallel, the joint being wider below (arrow). (Compare with Fig. 24*B*.)

In the cervical region, spurs at the disc margin present a very definite clinical problem. These may project laterally into the foramen or backward into the spinal canal. In the latter case the myelogram may simulate the picture of herniated cervical disc.

In some cadavers the intervertebral foramen of this region was almost completely occluded by these bony outgrowths, either projecting backward from the disc margin or forward from the posterior articulations.

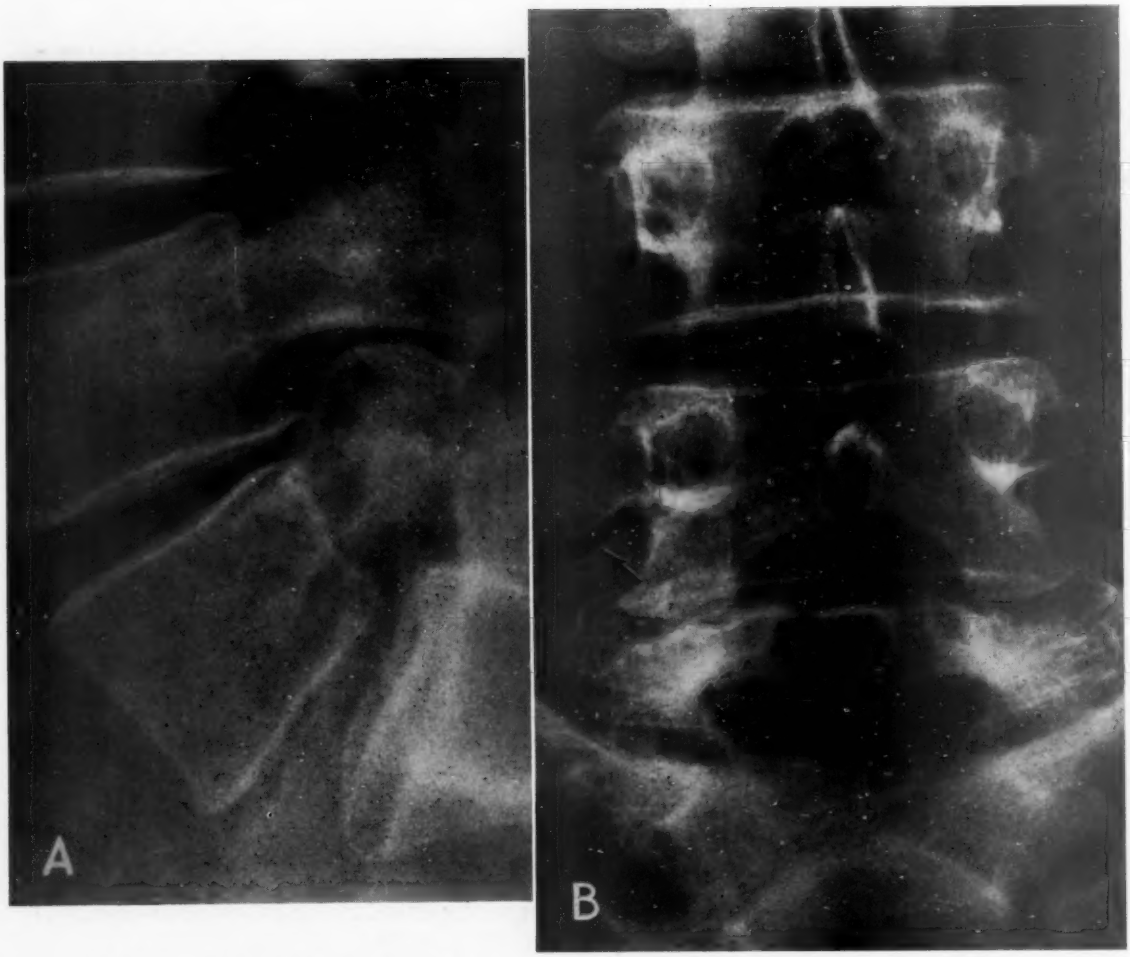


Fig. 19. Male, aged fifty-two. Low back pain with pain in both legs for several years. Dorsal kyphosis, lumbar lordosis, Achilles reflexes normal. (*A*) Break in 5th neural arch with 1st degree spondylolisthesis, foramen encroachment and lordosis. The increased lumbar curve has thrown increased stress upon the 4th pair of posterior articulations. The 4th disc is thinned posteriorly. There is a reverse spondylolisthesis of 4 backward on 5 and the 5th superior articular processes have subluxated forward and upward into the 4th foramen decreasing the size of that opening (4th articulation retouched). (*B*) Impingement between the 5th superior articular process and the 4th neural arch on the right side with development of a vicarious joint indicated by arrow (joint accentuated).

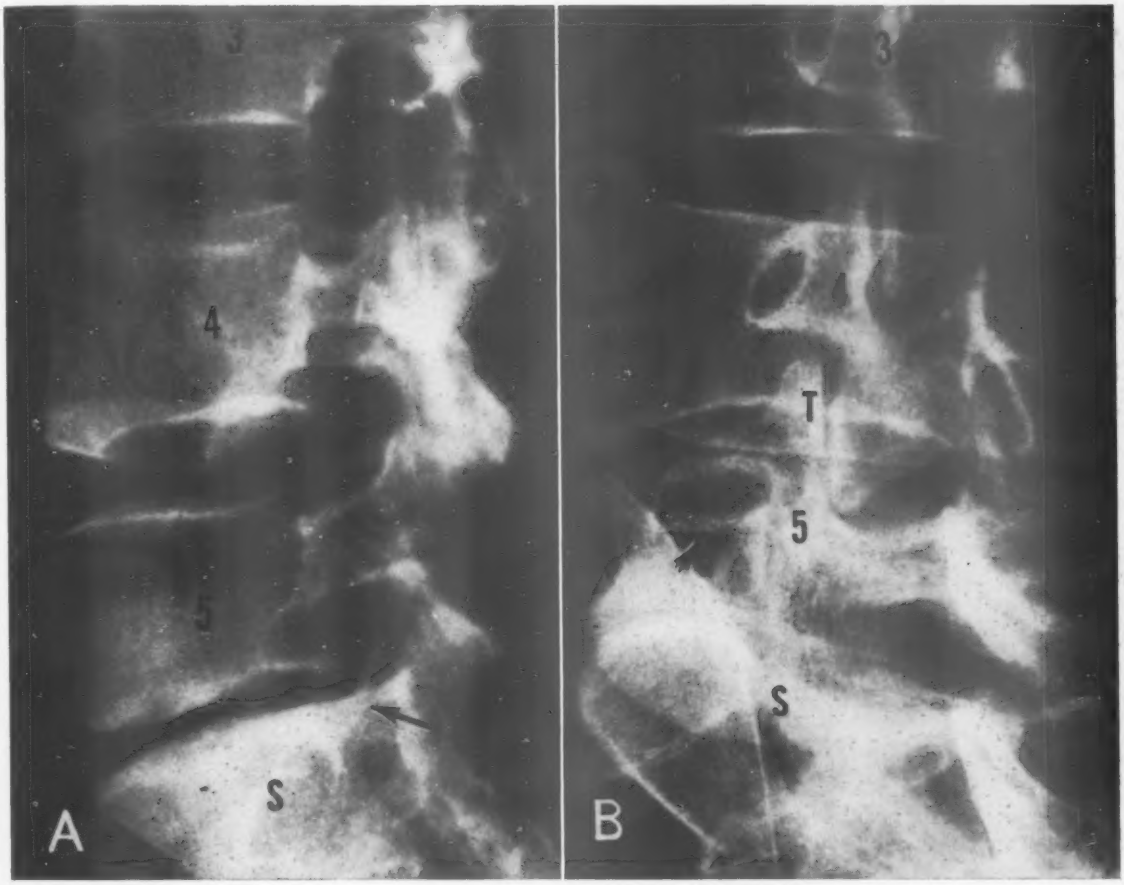


Fig. 20. Female, aged thirty-two. Pain in left hip, radiating down to left ankle. No history of injury. (*A*) The lateral view shows the commonly seen thinning of the 5th lumbar disc. There is encroachment of the 5th foramen. Foramina above this level are normal. (*B*) The 45° oblique view (pedicles accentuated) shows The 5th foramen smaller than normal (compare with Fig. 7). The articular process of the sacrum impinges against the under surface of the 5th pedicle between numeral *5* and the arrowhead. There is telescoping subluxation of the 4th posterior articulation (*T*) not evident in the lateral view. (Compare lateral view with Fig. 24*C*.)

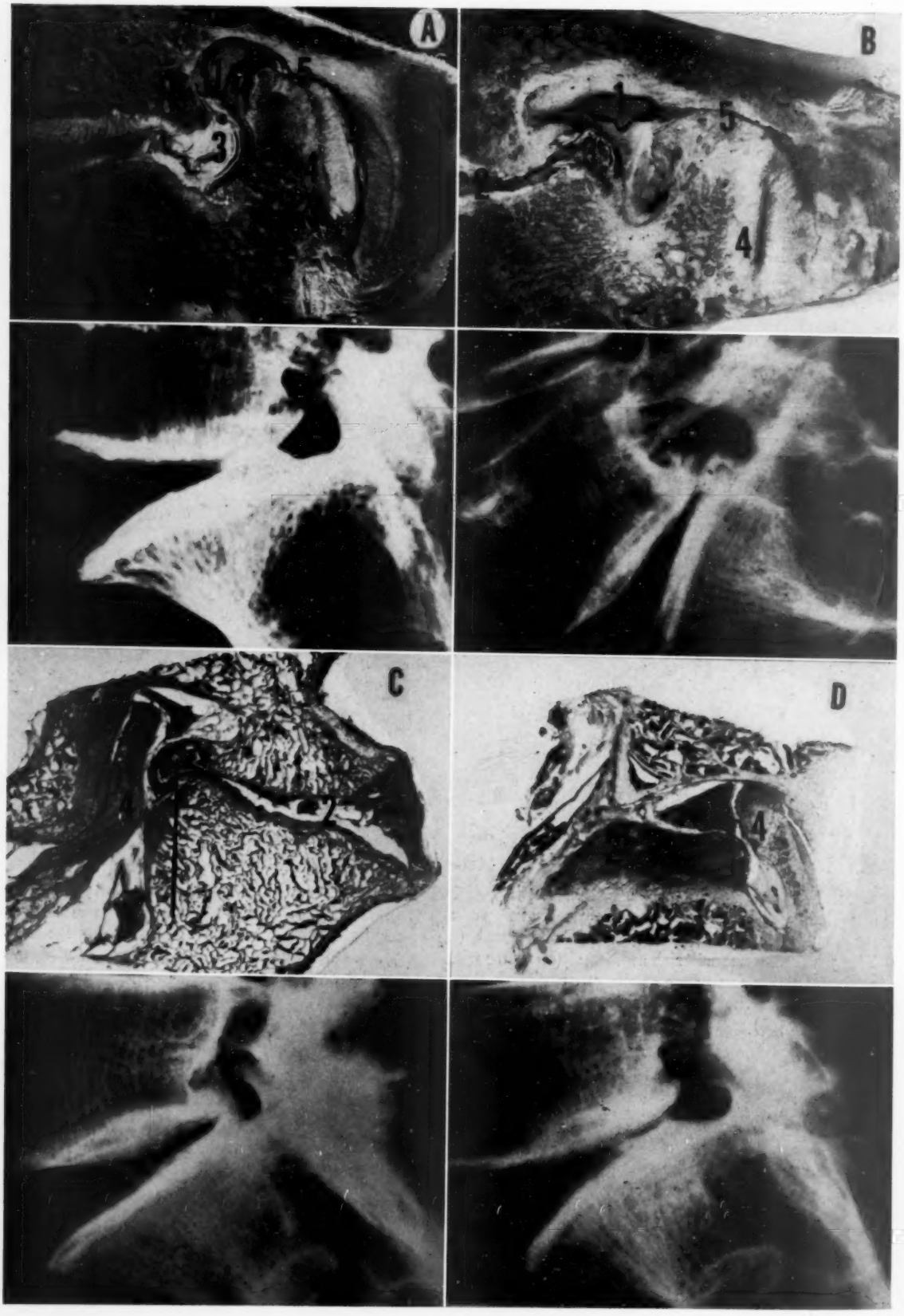


Fig. 21

These foramen encroachments secondary to disc thinning and spur formation must not be confused with herniations of disc substance unto the opening (Fig. 12, 13, 14, 15 and 16).

An arthritic process of the posterior articulations as shown by Gray[4] ordinarily is capable of causing root pressure but an osteoarthritis of the Marie-Strümpell type which may progress to complete ankylosis of the posterior joints may, in the absence of disc thinning, leave the foramen normal in size and shape.

Agenesis of the pedicle while theoretically causing an enlarged foramen may, as reported elsewhere,[6] actually produce foramen constriction and consequent nerve root pressure or displacement as a result of depression of the poorly supported neural arch.

As a result of disc degeneration and thinning, the foramen diameter may become decreased in several ways: The pedicles are brought more closely together decreasing the cephalocaudad diameter. Thickening or buckling of the ligamentum flavum often takes place. This ligament may even become ossified.

Because of the inclined plane of the posterior articulation, the lower vertebra may become wedged forward as the disc undergoes thinning. This reverse spondylolisthesis causes a decrease in the anteroposterior diameter of the foramen. The superior articular process from below subluxates upward and forward into the foramen, constricting the size of that opening (Fig. 10 and 11).

If subluxation of the posterior articulation becomes sufficiently pronounced, a bony impingement occurs between the tip of the superior articular process and the pedicle or transverse process above. There may also occur an impingement between the tip of the inferior articular process and the lamina of the arch below. With this impingement, there may develop a new articulation. Erosion and sclerosis of the underlying bone occurs, usually with hyperplastic bone spurs about the joint margin. These impingements are painful and the foramina are encroached upon (Fig. 17, 18, 19 and 20).

The vertebral bodies are not connected by a strong longitudinal ligament at the plane of the pedicles so that herniation of a

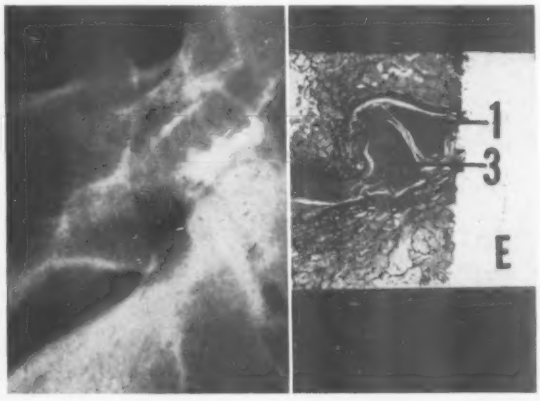


Fig. 21. Roentgenograms and corresponding sections or blocks of a group of encroached 5th lumbar foramina showing: *1*, distorted nerve; *2*, intervertebral disc; *3*, herniating disc substance; *4*, articular process subluxating upward from below; *5*, impingement of articular process with sclerosis. Photographs of blocks (*A*) and (*B*) are magnified $\times 1\frac{1}{2}$ and the nerve roots outlined. (*A*) shows the 5th vertebral body slightly posterior to the sacrum and because of the telescoping subluxation the articular cartilages do not register opposite each other. In (*B*) the 5th body, on the other hand, is in forward spondylolisthesis on the sacrum and marked sclerosis has occurred at the point of impingement beneath the 5th pedicle. (*C*) There is marked degeneration of the disc but the subluxated articular process has not impinged against the pedicle above. This section is reversed from the roentgenogram. (*D*) Section somewhat laterally. The nerve here is lying above the disc beneath the pedicle and pressed upon by the articular process which has indented its posterior surface. (*E*) In this section, like the previous one, the nerve section has become triangular as a result of pressure from three directions. A large herniation of disc substance is causing the pressure in this case. In both (*D*) and (*E*) the nerve has completely losts its surrounding cushion space. Upper end of line in (*C*) indicates herniating disc.

weakened disc, as described by Friberg,[3] may occur backward and laterally into the fixed bony ring of the foramen. This herniation of the disc into the foramen constitutes still another type of encroachment which merits recognition (Fig. 21*A*, *C* and *E*).

NERVE CHANGES INCIDENTAL TO FORAMEN CONSTRICTIONS

Macroscopically the compressed nerve may show some alteration in its shape, such as a flattening, concavity or triangulation incidental to the external pressure of bulg-

Fig. 22. Cadaver, aged eighty-three. Pain in the back but no history of sciatica obtainable. (*A*) Numerals indicate the posterior portion of each intervertebral disc. This man had a subluxation of the 4th and 5th posterior articulations with encroachment of the 4th foramen. Impingement of the 4th superior articular process against the under-surface of the 3rd pedicle is indicated by large arrow. Articulations and foramina above this point were normal. At the 5th posterior joint there is impingement of the sacral articular process against the undersurface of the 5th pedicle and a separate intra-articular ossicle indicated by the small arrowhead. Nerve roots *2*, *3* and *5* appear normal and are surrounded within the foramen by a generous cushion space. Nerve root *4*, however, is compressed and flattened by a decrease in the size of the foramen incidental to the posterior joint subluxation as well as a posterior herniation of the disc seen just above and behind the numeral *4*. Examination of the spinal canal at this level, showed a bulging of the 4th disc substance backward into the canal, displacing the 5th lumbar root. A postmortem myelogram revealed a corresponding filling defect in the oil column. Had intraspinal operation been done to relieve pressure upon the 5th root, the condition noted at the exit of the 4th foramen could hardly have benefited. (*B*) Oblique roentgenogram of this specimen showing subluxation and impingement of the 4th and 5th articulations.

ing disc substance. Exostoses or subluxation of a posterior joint will produce pressure upon the dorsal surface of the root. In each case, since the foramen is a complete bony ring, counter pressure is exerted by the remaining circumference of the opening (Fig. 22).

Fig. 22. (*C*) Fourth lumbar ganglion ×13 compressed by the 4th foramen encroachment. Many of the large ganglion cells were flattened.

(*D*) Fourth spinal nerve ×18 just distal to the ganglion shown in previous section but slightly greater magnification. Marked flattening of the nerve and its constituent bundles. The foramen encroachment resulted from herniation of disc substance into the opening shown in (*B*).

In certain cases there is a marked fibrosis and thickening of the epineurium which surrounds the entire nerve, firmly attaching the root to the foramen walls and extending inward between the different nerve bundles as the perineurium. Such a nerve must be removed by sharp dissection as contrasted to the normal nerve surrounded by its cushion space and easily removed from the foramen by blunt dissection (Fig. 25*B*).

Microscopically, various morphological changes and stages of nerve degeneration and regeneration were noted. Ganglion cells were found to be flattened. This flattening had also involved certain nerve bundles. Many Schwann tubules outlined by the neurilemma were empty of myelin and axones where the macrophages had removed these degenerated elements. In other sections of the same nerve bundle, these tubules were seen already filled with multiple rods of Schwann protoplasm and nuclei. This is said to represent a later stage in the process of nerve regeneration[7] (Fig. 23, 24 and 25).

The presence of nerve fibers much reduced in size, could, in certain cases at least, be taken as evidence of nerve regeneration.

Some evidence of edema of the endoneurium was observed (Fig. 25*F*). Hemorrhage beneath the perineurium was found involving numerous roots in one specimen having adhesions about those structures (Fig. 26). Sclerosis of arterioles within the nerve bundle was also observed (Fig. 25*C*).

DISCUSSION

Patients presenting the clinical picture of nerve root pressure are too often and without adequate study diagnosed as "herniated disc." This picture has come to be termed the "ruptured disc syndrome." These symptoms result from nerve root pressure or irritation. The condition is usually sought within the spinal canal while the less accessible intervertebral foramen may be inadequately explored. Herniation within the canal may exert pressure upon

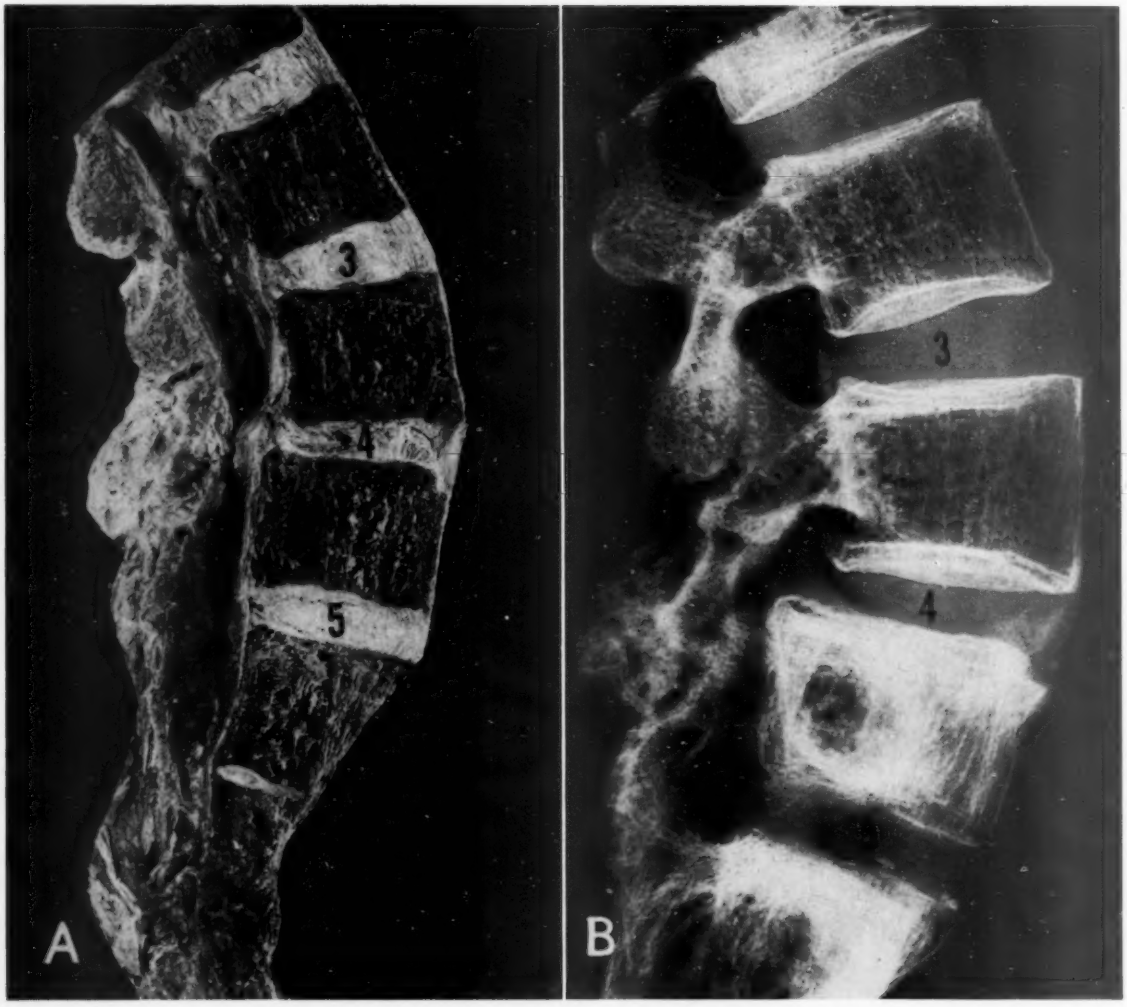


Fig. 23. (*A*) Sagittal section, left side, cadaver, male aged sixty-two. Pain in legs for eight years before death. Bulging of the 4th disc into spinal canal compressing the 5th lumbar nerve root and encroaching on the 4th foramen.

(*B*) Roentgenogram of same specimen, discs numbered. Spondylolisthesis of L_4 forward on L_5 but no break in the neural arch. This may happen, as here, when degeneration of a posterior articulation has taken place. Constriction of the 4th foramen is present. Again, operative removal of the herniated 4th disc from this spinal canal for relief of 5th root pressure would still have left decreased cushion space for the 4th root where it passes through the foramen.

a lower nerve root while producing adjacent foramen encroachment. For instance, the cadavers in Figures 22 and 23 showed herniation of the fourth disc backward into the spinal canal. In both cases the fifth root was displaced and would have shown a filling defect upon the myelogram. In each, the fourth foramen was encroached upon. Removal of the intraspinal hernia alone would not have relieved the foramen encroachment. Successful operative treatment necessitates not only removal of the hernia for distal root pressure, but also proper attention to the adjacent foramen constriction. The cause of nerve root pressure may be disc herniation, or, among others, radiculitis, trauma, tumor, malignancy, extradural abscess, osteomyelitis, and as shown above, constriction of the intervertebral foramen.

Duncan[2] has shown that gradual constriction of a nerve in young animals destroyed the myelin about the axone but did not completely destroy its function or produce paralysis. However, after six and a half months there was a significant decrease in the size of the limb muscles and a reduction in the number and size of the nerve fibers below the constriction.

Magnuson,[9] in discussing "the subject of low back pain accompanied by so-called sciatica," states that the "approach has been mainly from the standpoint of root pressure from a ruptured intervertebral disc." He states further "this viewpoint seems much too narrrow." "It is quite apparent that variations in the path of the nerves are frequent not only in the foramen but at the exit from the foramen. Where the nerve is bound down or the space through which it emerges is narrow a very little overstrain or inflammatory process in the ligaments through which the nerve makes its exit could cause definite symptoms of pressure on the involved branch."

The importance of intervertebral foramen encroachment at once becomes apparent in properly evaluating nerve root pressure.

Preliminary conservative management is most important and should be given a thorough trial before subjecting the patient to operative interference. If that becomes necessary, it is imperative that the surgeon consider not alone the spinal canal but also the intervertebral foramen as a possible site of the root pressure.

Williams and Yglesias,[13] Briggs and Krause,[1] Gray,[4] and Mitchell,[10] have relieved patients suffering from nerve root pressure by facetectomy (complete removal of the posterior articulation) decompressing the intervertebral foramen. Some of these patients were previously unrelieved by disc operations within the spinal canal.

Gray and Magnuson advise against curettement of the disc, a procedure which leaves the structure thinned and consequently results in further constriction of the foramen. With respect to foramen decompression, Briggs and Krause state that the disc substance bulging into the opening may be left undisturbed if counter pressure against the root by the posterior wall of the foramen is relieved by removal of the entire posterior articulation.

At any operation to relieve nerve root pressure, a very careful search within the intervertebral foramen even to its most lateral limits is always indicated.

SUMMARY

The anatomy of the intervertebral foramen allows a generous reserve safety cushion space about the nerve root. Within this space occur the compressible lymphatics, blood vessels, areolar and fatty tissue. The normal movements of the spine may produce a physiological constriction of the foramen amounting to as much as a third of its area. This explains the positions assumed by patients suffering from nerve root pressure and the reason for aggravation of their pain upon certain movements. Permanent constriction of the foramen from any cause reduces the reserve cushion space and predisposes to root pressure upon occurrence of edema, hemorrhage, perineural inflammation or additional foramen encroachment. Foramen constriction

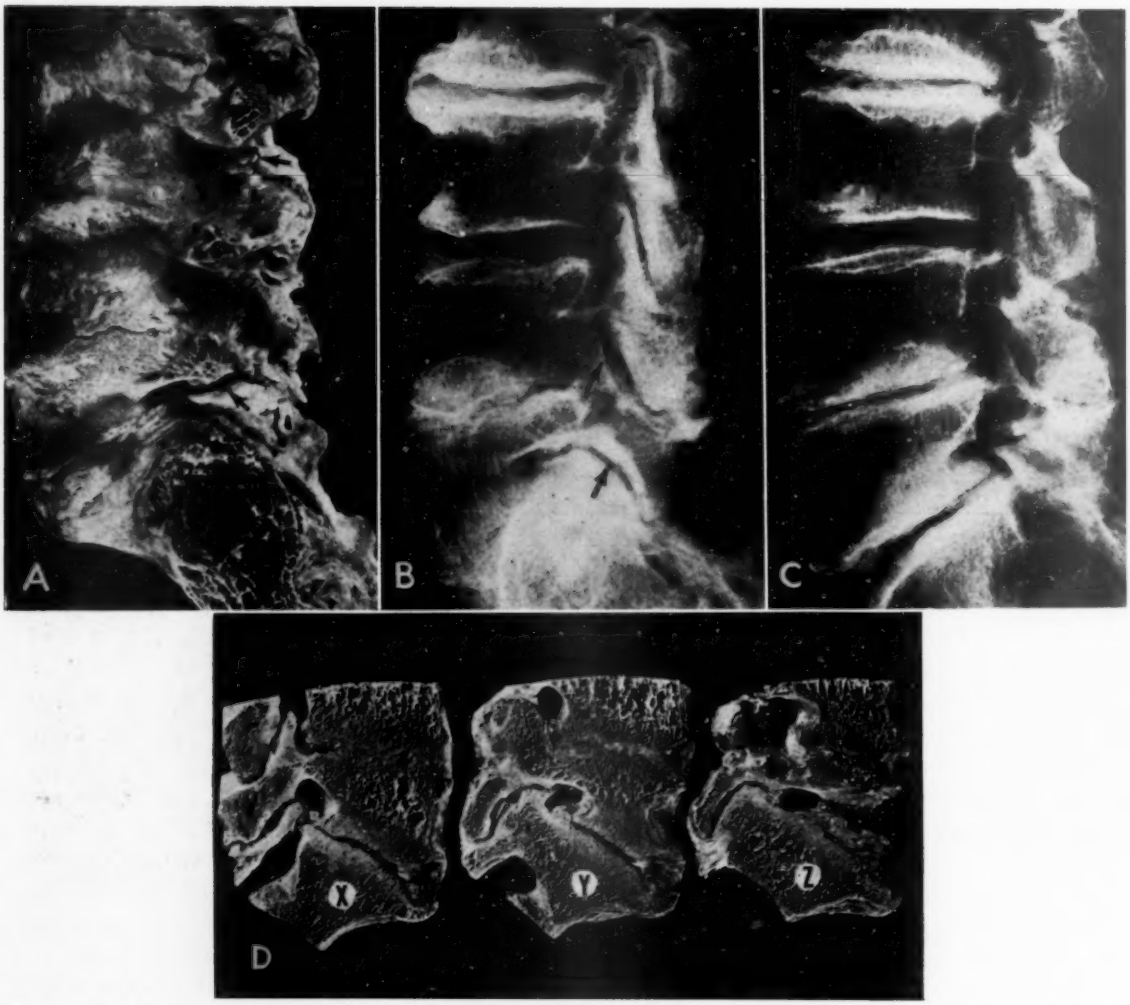
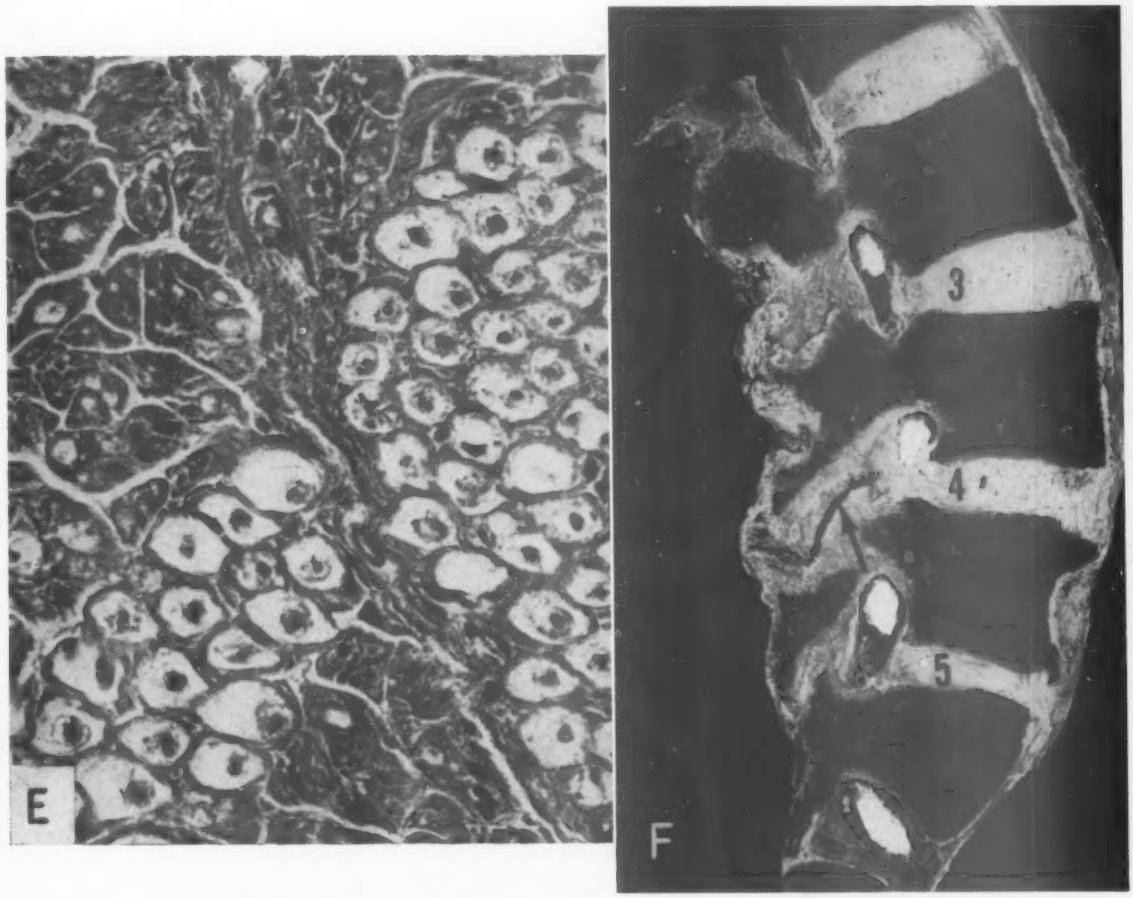


Fig. 24. (*A*) Male cadaver, aged seventy-five. Had complained of pain in the right leg. The photograph shows impingement of the articular processes (arrows) and encroachment of the 5th lumbar foramen.

(*B*) 45° oblique roentgenogram and (*C*) the lateral view show disc degeneration with thinning. There is sclerosis of those vertebral bodies where the discs are thinned, although the 3rd disc is only slightly involved. Telescoping subluxation of the posterior articular processes with impingement has occurred as a result of this degenerative process. Dissection revealed encroachment of the 5th intervertebral foramen with compression and flattening of the nerve root. This structure was firmly attached to the foramen walls by a mass of dense fibrous tissue (Fig. 25*A*).

(*D*) Serial sections of the right, 4th and 5th foramina, opposite side same cadaver (side of patient's sciatica). *X*, medial section. Articular process from sacrum subluxated upward into 5th foramen which is encroached upon. Fourth and 5th discs thinned with sclerosis of adjacent vertebral bone especially the 5th posteriorly as a result of pressure uncushioned by disc substance. *Y*, middle section. Note impingement of sacral articular process against the under surface of the 5th pedicle with bony sclerosis at this point. *Z*, lateral section. Impingement and foramen constriction present to the lateral plane of this vertebra and its foramen. This is the final stage of disc degeneration.



(*E*) Section of 5th lumbar root. This root was compressed between the 4th disc hernia and the dorsal wall of the spinal canal. This section, ×650, shows evidence of probable nerve degeneration one space below the disc herniation. This high power section, distal to the ganglion, shows normal nerve fibers on the right side and the lower left corner. Elsewhere there were patches of degenerative change, vacuolation, also multiple nuclei in the same tubule. The 5th foramen was not encroached as seen in (*B*). The herniated disc at L_4 pressed against the 5th root. The patchy degenerative changes distal to the 5th ganglion here visualized may have resulted from that pressure.

(*F*) Section through foramina on right side, same cadaver, showing subluxation, impingement and sclerosis of the 4th posterior articulation (arrow). The 4th foramen is encroached upon while the other foramina show ample cushion space about the nerve roots.

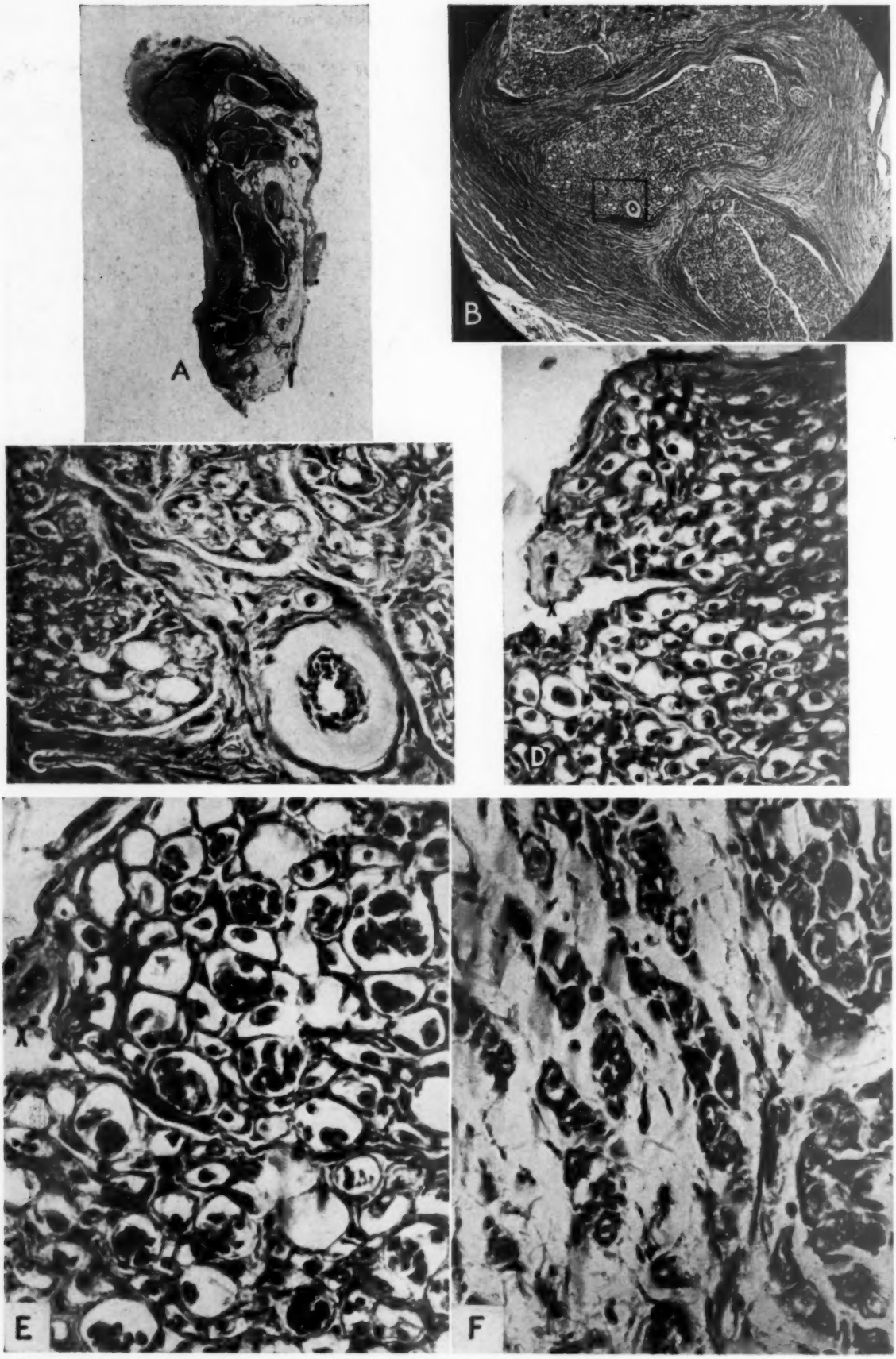


FIG. 25

may result from various causes but the most common is disc degeneration and its secondary changes. These include: herniation of disc substance into the foramen, thinning of the disc with approximation of the pedicles, subluxation of the upper vertebra forward or backward upon the one beneath, hyperplasia of the ligamentum flavum, bony spur formation projecting backward from the disc or forward from the posterior joint, and lastly, subluxation of the articular process from below upward and forward into the foramen. Bony impingement of the tip of the articular process may occur with development of erosion and sclerosis at the point of contact. Nerve roots removed from constricted foramina have shown definite degenerative changes in their morphology.

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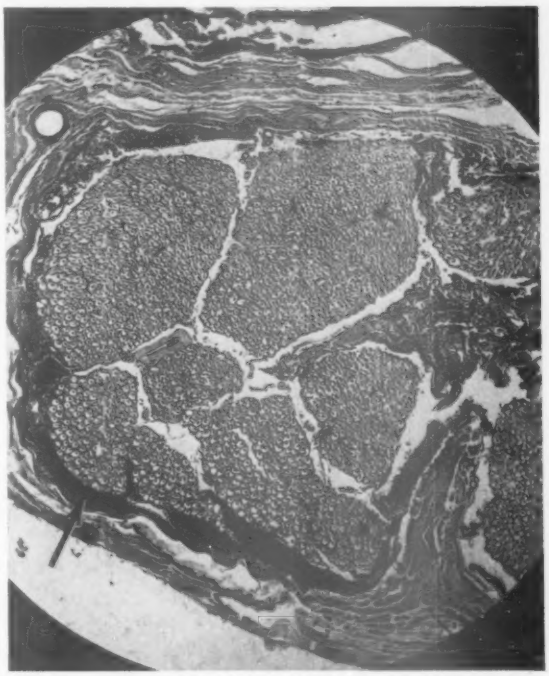

FIG. 26. Male cadaver, aged eighty-five. Fibrotic changes about nerve roots. Nerves adherent to foramina. Section from a lumbar nerve root, ×75, showing a nerve bundle surrounded by subperineural hemorrhage (arrow). Same individual as in Figure 13.

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FIG. 25. (*A*) ×7.7. This section of the left 5th lumbar root, removed by sharp dissection, is distal to the ganglion. It shows a concavity from pressure of the 5th intervertebral disc. Some of the nerve bundles are flattened and there is hyperplasia of the epineurium and perineurium at the upper portion of the root.

(*B*) ×48.8. Somewhat greater magnification of field indicated by circle on previous section. Note hyperplasia of fibrous tissue. Some of the nerves have been destroyed leaving empty Schwann tubules. A sclerotic intraneural arteriole is seen near the center of the section.

(*C*) ×424. Greater magnification of field indicated on previous section. To the left of the sclerotic arteriole appear two empty Schwann tubules outlined by their neurolemma.

(*D*) and (*E*) ×419. These are both high power sections from the same 5th left lumbar nerve bundle but proximal to the ganglion and taken only a few millimeters apart. The same arteriole (*X*) is noted to the left of each section. (*D*) ×419 shows nearly all of the nerves normal in transverse section. In (*E*) ×524 most of the same nerves show evidence of degeneration. Many Schwann tubules are swollen, some are empty and others are filled with multiple rods of Schwann cytoplasm. In one of these tubules nine distinct nuclei are visualized.

These sections seem to demonstrate that a nerve bundle may apparently exhibit different stages of degeneration or normality at points only a few millimeters apart.

(*F*) Section, ×524, taken from the 5th left motor root lying between the ganglion and the 5th disc. Separation of nerve fibers and endoneural spaces enlarged. Appearance suggests possible edema of endoneurium.

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SKELETAL DEVELOPMENT IN INFANCY

STANDARDS FOR CLINICAL USE*

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THIS paper presents standards by which the skeletal development of the infant may readily be assessed. The standards to be described are of two kinds:

(1) Tables, based on the number of ossification centers which may be seen in roentgenograms of either the hand or foot, at 10 age-levels between birth and 3 years.

(2) Tables, based on the presence or absence of specific ossification centers at these same age-levels, serving as a further check on infants suspected of unusually retarded skeletal development.

These two types of standards may be used either separately or together. The first method provides essentially a routine check on skeletal development of the infant. The second method offers a clinical tool in the diagnosis of those conditions, such as athyreotic cretinism, which are accompanied by marked retardation in the appearance of ossification centers.

In the construction of these tables, we are largely indebted to the earlier research of Pyle and Sontag,[15] which Leonard[11] has said appears to be "as accurate a summary of the stages of development as can be compiled from closely grouped serial roentgenograms of carefully selected normal children" (p. 55).

LITERATURE

Many studies have been concerned with some aspect of the onset of ossification of primary and secondary epiphyses in the body. Reviews of earlier literature have been given by Flory,[5] Sontag, Snell and Anderson,[25] Leonard,[11] and Kelly and L. Reynolds.[9]

Recent research in this area has dealt with such factors as *time* of appearance of specific centers;[1,4,15] *number* of centers present in the body as a whole or in parts of the body, at different age-levels;[25] *sequence* of appearance of centers;[23] genetic,[17] seasonal[18] and racial[9] aspects of onset of ossification; and the relation of beginning ossification to various metabolic, endocrine and health problems of the infant and child.[2,3,6,7,22]

There have been various attempts to put our present knowledge to better clinical use. Methods which have been offered in the last few years include the use of skeletal atlases;[5,14,26] tables and charts representing means and measures of variability;[15,25] tables based on the 80th percentile;[8] groupings based on factor analysis;[20] the use of the Fels Composite Sheet;[19,24] the ossification index devised by Leonard;[11] the bone quotient (bone age /chronological age) suggested by Lurie, Levy and Lurie;[12] and the "red graph method" originated by Pyle, *et al.*,[13,16] concerned with the range between the fastest and slowest maturing centers in an area.

Each of these methods has contributed to some extent to the clinical assessment of skeletal development in infants. However, it seems fair to say that each method either is not made for use with infants,[12] or to a greater or lesser degree involves manipulations, calculations or interpretations which limit its use by the busy clinician.

THE PRESENT STUDY

The first method here described requires a knowledge of the age and sex of the child, and a roentgenogram of the hand (or foot, see below). The number of ossification centers present in the hand and wrist are counted, and an estimate of skeletal status

* From the Fels Research Institute for the Study of Human Development, Antioch College.

TABLE I

SKELETAL DEVELOPMENT OF HAND, BASED ON NUMBER OF OSSIFICATION CENTERS PRESENT AT VARIOUS AGE-LEVELS, FROM BIRTH THROUGH 3 YEARS

Development of Hand	Age in Months									
	Birth	1	3	6	9	12	18	24	30	36
					Boys					
Very fast	1–2	2	3	3–5	5–9	8–14	16–19	21–23	23	24
Fast	0	1–2	2	2	3–4	5–7	10–15	16–20	21–22	23
Average	0	0	1–2	2	2	3–4	6–9	12–15	16–20	19–22
Slow	0	0	0–1	2	2	2	4–5	8–11	13–15	16–18
Very slow	0	0	0	0–1	0–1	1	1–3	1–7	5–12	6–15
					Girls					
Very fast	2–3	3	3–4	4–8	11–13	16–18	22–24	24–25	25–26	26–27
Fast	0–1	2	2	3	6–10	12–15	20–21	23	24	25
Average	0	0–1	2	2	3–5	6–11	14–19	20–22	22–23	23–24
Slow	0	0	1–2	2	2	3–5	12–13	17–19	20–21	22
Very slow	0	0	0	0–1	2	2	2–11	6–16	14–19	17–21

read from Table 1. For instance, a 24 month old boy with 13 centers in his hand and wrist is classed as "average" by Table 1. However, a 24 month old girl with 13 centers is classed as "very slow." The well known sex differences in ossification, an important factor in any analysis of skeletal development, are thus taken into consideration in the table.

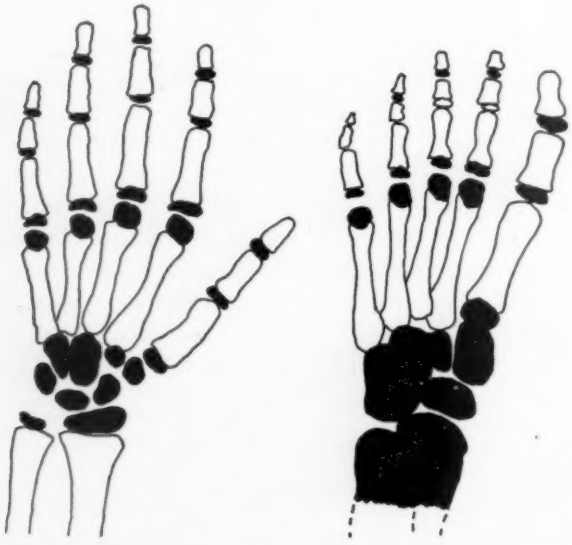

FIG. 1. The solid areas represent the 28 centers of ossification counted in the hand, and the 21 centers counted in the foot.

The 28 centers considered in the hand and wrist are: 7 carpals (pisiform not included), the 5 metacarpal and 14 phalangeal epiphyses, and the distal centers for radius and ulna (Fig. 1).

The descriptive classifications shown in Table 1 have precise statistical meanings:

Very Fast: In any age-sex group (e.g., 24 month old boys), the 10 per cent having the most centers present.

Fast: The 20 per cent of this group below the very fast category.

Average: The middle 40 per cent of the group.

Slow: The 20 per cent below the average category.

Very Slow: The 10 per cent of the group having the fewest number of centers present.

These classifications were derived from the actual distribution of ossification centers in 58 boys and 61 girls, healthy white infants participating in the longitudinal growth program of the Fels Research Institute.[21] Each of these infants has had 10 roentgenograms of the hand taken, one at

each age-level shown in Table I, and the table is based on the actual distribution of these cases. The table thus represents an analysis of approximately 1,200 roentgenograms of the hand.

If an individual infant, when examined by the physician, has either more or fewer ossification centers present at a certain age-level than are shown in Table I, that infant has more or fewer centers than were shown by any of the normal infants used as a standard. Thus, if a girl at 24 months has only 4 centers in the hand and wrist, she has fewer centers at this age than any of the 61 girls in the Fels series; if, at this age, a girl infant has 27 centers, she has more centers than the most advanced Fels girl at 24 months.

The classifications, therefore, provide a quick and convenient method of describing the skeletal status of the infant, but the physician, knowing the statistical interpretation of these terms, may make his own classification.

In similar manner to the hand, a roentgenogram of the foot may also be used to assay the skeletal development of the infant (Table II). In assaying the foot, the following 21 centers are considered (Fig. 1): 7 tarsals, epiphyses for the 5 metatarsals, and epiphyses for the 5 proximal phalanges and the distal phalanges of all but the fifth toe. Not included, because of their inconstant nature,[15] are the epiphyses for the middle phalanges and for the distal phalanx of the fifth toe. The ends of the long bones, and the epiphysis of the calcaneus, not easily seen in an anteroposterior roentgenogram of the foot, are also not considered.

TABLE II

SKELETAL DEVELOPMENT OF FOOT, BASED ON NUMBER OF OSSIFICATION CENTERS PRESENT AT VARIOUS AGE-LEVELS, FROM BIRTH THROUGH 3 YEARS

Development of Foot	Age in Months									
	Birth	1	3	6	9	12	18	24	30	36
					Boys					
Very fast	3	4	4	6	6–8	6–10	9–12	13–16	16–17	17–18
Fast	3	3	4	4–5	4–5	5	8	11–12	14–15	16
Average	2–3	3	3–4	4	4	4	6–7	9–10	11–13	14–15
Slow	2	2–3	3	3–4	4	4	5	7–8	9–10	12–13
Very slow	2	2	3	3	3	3	3–4	3–6	7–8	8–11
					Girls					
Very fast	4	4	4	5–7	8–11	10–12	15–16	18–21	21	21
Fast	3–4	3–4	4	4	6–7	9	13–14	16–17	19–20	21
Average	3–4	3	3–4	4	4–5	6–8	10–12	13–15	16–18	18–20
Slow	2	3	3	4	4	5	8–9	11–12	14–15	16–17
Very slow	2	2	3	3	3	4	4–7	6–10	10–13	11–15

The second method of assaying skeletal development in the infant, to be described below, is indicated when a first estimate, based on the study of hand or foot (Table I or II), leads the physician to suspect marked retardation in skeletal development of his patient.

In Table III, data are given for 8 centers of ossification, none of which are considered in Table I or II. For each center, the average age at appearance is given, together with the age when, in the absence of that center, the development of an individual infant may be considered as "slow" or "very slow."

For example, in boys, the head of the femur, as seen in a roentgenogram of the hip, appears on the average at 4.4 months of

age. If, in a boy infant of 6 months, this center has not yet appeared, the development of that infant in this characteristic is slow. If, in a boy infant of 9 months, this center has not yet appeared, the infant is classed as very slow. Separate tables are given for boys and girls.

Table III also has precise statistical meanings, as shown in Table IV. In the example given above, the head of the femur has appeared, by six months of age, in 86 per cent of the Fels normal series of boys. The center has appeared in 97 per cent of this group by 9 months. Thus, knowing the figures on which the verbal descriptions are based, a physician may make his own interpretation of the significance of his findings.

TABLE III

SKELETAL DEVELOPMENT OF BODY, BASED ON ABSENCE OF INDIVIDUAL CENTERS OF OSSIFICATION

Ossification Center	Average Age at Appearance (mo.)	Skeletal Development	
		Slow (Has not appeared by age indicated)	Very Slow (Has not appeared by age indicated)
	Boys		
Distal femur	Prenatal	—	Birth or later
Proximal tibia	Prenatal	Birth	1 mo. or later
Head of humerus	0.7	1 mo.	3 mo. or later
Distal tibia	3.9	6 mo.	9 mo. or later
Head of femur	4.4	6 mo.	9 mo. or later
Capitellum	6.3	9 mo.	12 mo. or later
Gt. tub. humerus	11.4	18 mo.	24 mo. or later
Distal fibula	12.5	18 mo.	24 mo. or later
	Girls		
Distal femur	Prenatal	—	Birth or later
Proximal tibia	Prenatal	Birth	1 mo. or later
Head of humerus	0.9	1 mo.	3 mo. or later
Distal tibia	3.4	—	6 mo. or later
Head of femur	3.7	6 mo.	9 mo. or later
Capitellum	4.1	6 mo.	9 mo. or later
Gt. tub. humerus	6.6	9 mo.	12 mo. or later
Distal fibula	9.3	12 mo.	18 mo. or later

DISCUSSION

We have described two methods of assaying the skeletal development of infants. One method employs a roentgenogram of either hand or foot, and is based on the number of centers present at various age-levels between birth and three years. The second method is based on the time of appearance of 8 ossification centers, none of them in the hand or foot. The need for this additional standard becomes obvious, when we consider the pattern of appearance of ossification centers during early infancy.

In boys, 12 centers of ossification are normally expected to appear, on both right and left sides, during the first postnatal year.[15] Two of these centers have been included in the hand standard, Table 1; and 2 (together with calcaneus and talus, normally prenatal) are included in the foot standard, Table II. The other 8 centers, however, appear elsewhere throughout the body.

Thus, during early infancy in boys (and to a lesser extent in girls), there are very

few centers available in hand or foot, on which to base a standard. This presents no particular problem when dealing with children whose skeletal development is normal or advanced. When, however, preliminary screening reveals retarded skeletal development in a young infant, Table III should be used for a more thorough check.

Particularly in young infants where a suspected thyroid deficiency may exist, and where, as Kennedy[10] says, a satisfactory prognosis depends on early recognition and treatment, the use of both standards is indicated.

Table IV

PERCENTAGE OF NORMAL FELS SERIES HAVING INDIVIDUAL CENTERS PRESENT AT VARIOUS AGE-LEVELS

Ossification Center	Age in Months									
	Birth	1	3	6	9	12	18	24	30	36
Boys										
Distal femur	98	100								
Proximal tibia	84	98	100							
Head of humerus	36	72	98	100						
Distal tibia		3	36	93	100					
Head of femur		2	22	86	97	100				
Capitellum			31	72	86	97	97	98	100	
Gt. tub. humerus				24	47	69	86	95	98	98
Distal fibula				3	31	55	90	98	100	
Girls										
Distal femur	98	100								
Proximal tibia	88	100								
Head of humerus	38	77	100							
Distal tibia	2	10	46	100						
Head of femur	3	10	46	97	100					
Capitellum		3	54	90	98	100				
Gt. tub. humerus			12	52	90	95	100			
Distal fibula				16	62	92	98	100		

THE RELATION OF HAND OR FOOT TO BODY AS A WHOLE

It is recognized that a physician will seldom have the roentgenograms available for an over-all estimate of skeletal status. A roentgenogram of the hand or foot, or both, will most commonly be used. It becomes important, therefore, to know how well the hand or foot represents the body as a whole.

In most studies, the hand has been used as a representative area. Sontag, Snell and Anderson,[25] however, cautioned against a too uncritical acceptance of the assumption that "as the hand grows, so grows the entire skeleton" (p. 951).

In the normal series here used, roentgenograms of the following areas, in addition to hand and foot, are available: lateral foot, shoulder, hip, and two views each of lower leg, knee, elbow. A total of 63 centers are considered in estimating the skeletal status of each infant, all from the left side of the body. Each child has been classified by hand, foot and total body at 1, 2 and 3 years of age. In Table V, comparisons are shown between hand and total body, and foot and total body.

In 357 ratings of skeletal development of the hand, as compared with ratings of the body as a whole in the same infant, 5

cases show marked disagreement. That is to say, in 5 cases (1.4 per cent) an examination of the hand gives a rating of skeletal development which is quite unrepresentative of the body as a whole. In 248 cases (69.5 per cent), the ratings for hand and body agree exactly, and in 104 cases (29.1 per cent), the ratings agree within one category.

In a similar comparison between the foot and the body as a whole, 6 cases (1.7 per cent) are markedly dissimilar. In 227 cases (63.6 per cent), there is complete agreement, and in 124 cases (34.7 per cent), ratings are in adjacent categories.

If these figures are accepted as representative, it may be concluded that between 60 and 70 per cent of the ratings made on either hand or foot will give a classification of skeletal status which is the same as that which would be obtained if roentgenograms of the whole body were available; between 30 and 35 per cent of the ratings will agree within one category; and between 1 and 2 per cent of the ratings will be completely unrepresentative.

A further examination was made in terms of the coefficient of correlation (r) between actual number of centers present in hand and in total body, and in foot and in total body, at each of the three age-levels considered above. The results are shown in Table VI, and support the conclusions reached from a study of Table V.

Table V

AGREEMENT BETWEEN RATINGS OF SKELETAL DEVELOPMENT FOR HAND, FOOT AND BODY, AT THREE AGE-LEVELS

Sex	Age	No. Cases	Complete Agreement	Agreement within One Category	Disagreement
		Comparison of Ratings for Hand and Body			
Male	1 yr.	58	37	21	0
Male	2 yr.	58	46	12	0
Male	3 yr.	58	40	17	1
Female	1 yr.	61	53	8	0
Female	2 yr.	61	36	24	1
Female	3 yr.	61	36	22	3
Totals		357	248	104	5
Per cent			69.5	29.1	1.4
		Comparison of Ratings for Foot and Body			
Male	1 yr.	58	33	22	3
Male	2 yr.	58	35	23	0
Male	3 yr.	58	39	18	1
Female	1 yr.	61	39	21	1
Female	2 yr.	61	36	24	1
Female	3 yr.	61	45	16	0
Totals		357	227	124	6
Per cent			63.6	34.7	1.7

SUMMARY

Standards are presented by which the skeletal development of the infant may be assessed. Assessments may be made from a roentgenogram of either hand or foot, or from a standard based on the time of appearance of specific centers of ossification. Both types of standards are con-

TABLE VI

COEFFICIENTS OF CORRELATION (r) BETWEEN HAND, FOOT AND BODY, BASED ON NUMBER OF OSSIFICATION CENTERS PRESENT*

Sex	Age	No. Cases	Hand-Body	Foot-Body	Hand-Foot
Male	1 yr.	58	.96	.86	.77
Male	2 yr.	58	.96	.91	.78
Male	3 yr.	58	.95	.90	.75
Female	1 yr.	61	.98	.88	.78
Female	2 yr.	61	.90	.91	.67
Female	3 yr.	61	.76	.92	.60

* All values are positive.

structed from an analysis of the actual time of appearance of 63 centers of ossification, in 119 normal infants, at 10 age-levels between birth and 3 years.

The descriptive classifications used are interpreted statistically, and an examination is made of the degree to which the skeletal development of the hand or foot is representative of the development of the body as a whole.

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INTRAVENOUS NEPHROGRAPHY: A METHOD OF ROENTGEN VISUALIZATION OF THE KIDNEY*†

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THE term nephrography is used to designate the roentgenologic contrast visualization of the kidney parenchyma. It is to be distinguished from intravenous urography or pyelography, in which the kidney pelvis and ureter, rather than the kidney substance itself, are opacified. A method for the production of nephrograms by the intravenous injection of contrast medium is the subject of the present report.

For some time it has been noted that intravenous urography produces an opacification of the kidney in patients with acute obstruction of the ureter. This phenomenon, resulting in a so-called nephrogram, was first described by Wesson and Fulmer[10] and later by Wilcox,[11] who also undertook experimental studies to determine the mechanism of the opacification. In a recently reported group of patients with acute renal colic, it was found that the involved kidney was opacified in 10 of 23 patients subjected to intravenous urography.[3]

Because acute ureteral obstruction due to disease enabled one to obtain a nephrogram, Weens and Florence[8] attempted to obtain nephrograms in any type of patient by purposefully producing temporary ureteral obstruction. External pressure to the abdomen was not found to be effective, but the obstruction of the ureter by an inflatable balloon-tipped ureteral catheter (Dourmashkin dilating bougie) enabled them to produce satisfactory visualization of the kidney. The procedure was not entirely practical, however, because of the instrumentation required and the discomfort produced by the ureteral obstruction.

Striking contrast visualization of the kidney and the aorta may be obtained by the injection of contrast medium directly into the aorta. This technique, called abdominal aortography, was first introduced by Dos Santos[1] and subsequently used by several others.[2,4] The method requires the direct and rapid injection of radiopaque material into the aorta under high pressure. Unfortunately, the procedure necessitates general anesthesia and the technical aspects are complicated.

During the course of our studies on the cardiovascular system by the technique of angiocardiography,[5] it was found that excellent opacifications of the kidney parenchyma could be produced. Steinberg and Robb[6] had previously mentioned this phenomenon in one of their reports on angiocardiography, but we have not been able to find any further observations. The present communication deals with contrast visualization of the kidney as produced by the intravenous injection of diodrast.

METHOD

The technique utilized in the present studies is fundamentally that described previously for angiocardiography.[5] The procedure consists of the rapid intravenous injection of 50 cc. of 70 per cent diodrast,‡ followed at proper intervals by a rapid series of roentgenograms of the kidney area.

The only preliminary medication is a cathartic the night before and generally an oral sedative, such as 0.1 gm. pentobarbital shortly before the procedure is undertaken. Since the diodrast may cause vomiting, the patient should abstain from food for at least three hours before the examination. A test film of the kidney area

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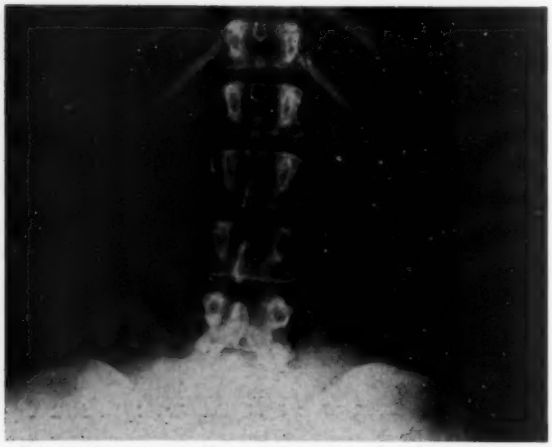

FIG. 1. Film study of the kidney area before obtaining nephrogram.

is obtained, and if excessive amounts of gas are in the colon, pitressin may be of value.

Before injection of the contrast medium a careful history for sensitivity to iodine is obtained. Nephrograms are not attempted in those patients who have evidence of poor renal function. If the history is not remarkable, a test dose of diodrast is injected. A test solution is prepared by diluting a drop of 70 per cent diodrast to 10 cc. with physiologic saline solution, and a small quantity of this mixture is administered intravenously. The needle is left in position, and if no reaction occurs within a few minutes, the remainder of the diluted material is injected. The patient is then observed for any untoward response.

The actual injection of the diodrast for the nephrogram must be made extremely rapidly to obtain a satisfactory result, requiring no more than two seconds to inject the usual dose of 50 cc. The syringe designed by Robb and Steinberg[5] for angiocardiography is of great value in that the caliber of the outlet is greater than that of an ordinary 50 cc. syringe. The injection is made through a 12 gauge needle or through a short length of catheter of similar bore inserted into an antecubital vein, preferably the basilic. If the vein is not large, the most satisfactory procedure is open exposure of the vessel through a small incision and direct insertion of the catheter. A rapid injection of saline solution may be used to test for extravasation and ease of flow. The arm used for the injection should be held in an elevated and abducted position, so that drainage will be more complete and rapid.

Serial roentgenograms of the kidney region are begun six seconds after the completion of the injection. These are ordinarily anteroposterior views, but oblique projections are useful in depicting the anterior and posterior surfaces of the kidney. A special table equipped with a built-in rapid cassette changer and self-recocking Potter-Bucky diaphragm has been used for the present studies. This makes possible the obtaining of rapid serial roentgenograms during the next fifteen seconds. As our results indicate, a single film taken fifteen to eighteen seconds after injection will almost always demonstrate satisfactory renal opacification. Hence, the procedure can be carried out without any special roentgenographic equipment. If an abdominal film is obtained several minutes after the injection, excretory pyelograms will be obtained.

RESULTS

Observations have been made on 35 patients, most of whom had no evidence of intrinsic renal disease. In 29 patients (83 per cent) a satisfactory degree of opacification of the kidney was obtained (Fig. 1 and 2). In the kidney it began as early as six seconds (1 instance with an unusually rapid circulation time) or as late as fifteen seconds following the injection of the contrast medium. In the majority of patients, however, beginning opacification was noted from nine to twelve seconds

FIG. 2. Film study of the kidney fifteen seconds following rapid injection of 70 per cent diodrast solution. Note opacification of both kidneys.

after injection. The maximum degree of contrast usually occurred approximately fifteen to eighteen seconds following injection. In general, the cortex attained greater density than the medulla (Fig. 3). The renal hilus and its major blood vessels were often clearly visible. The opacification faded rapidly, and in those instances where observations were made, it had almost entirely disappeared by sixty seconds after the injection. Several minutes later the contrast medium was demonstrable in the renal pelvis and ureter.

In 6 patients (17 per cent) satisfactory opacification of the kidney was not obtained. In 4 of these it was probably due to faulty injection and inability to get an adequate amount of diodrast into the vascular system in a short period of time. In 2 instances the reason for the unsatisfactory result was not apparent.

Often the aorta and larger arteries of the abdomen could be clearly defined before maximal opacification of the kidneys was noted (Fig. 4).

Fig. 4. Film study of the abdomen twelve seconds after the injection of contrast medium. Note opacification of aorta and its branches. The kidneys are less well opacified than on films a few seconds later.

DISCUSSION

The cause of the nephrographic effect seen in patients with ureteral obstruction has been discussed in detail elsewhere.[8,11] In contrast to the type of renal opacification produced in our studies, the nephrogram in patients with ureteral obstruction is obtained considerably later after injection of the contrast medium. The time interval may be as much as fifteen to thirty minutes. A considerable degree of opacification is attained only in the involved kidney. Since the amount of contrast medium is the same in the blood going to both the opacified and non-opacified kidney, it has been presumed that under these circumstances the nephrographic effect must be due to the presence of diodrast in the finer ramifications of the renal tubular system.

Fig. 3. Nephrograms of left kidney and medial part of right kidney. Although partly obscured by gas shadows, the greater density of the cortical area can be detected.

It is apparent that soon after injection the blood contains considerable contrast medium; hence, one sees the aorta and renal arteries. Since the opacification occurs early and disappears rapidly, it is felt that the presence of diodrast in blood is a major factor in the renal opacification, but some contribution may be made by diodrast in

the glomerular filtrate and tubular contents.

The procedure of intravenous nephrography is relatively simple compared with the other methods of obtaining contrast visualization of the kidney, such as obstructive nephrography or direct aortography. Only occasionally will there be any difficulty in obtaining a sufficiently rapid injection. No serious reactions have been noted in our relatively small series of observations.

At the present time our studies have been largely confined to an exploration of the possibilities of the technique and an investigation of modifications to improve it. Considerable interest has been aroused by the recent reports of Trueta *et al.*[7] demonstrating a by-pass in the renal circulation and, consequently, the shunting of blood away from the renal cortex under certain conditions. Their studies were carried out in animals, utilizing a technique similar to that reported here. Observations are being made, utilizing the nephrographic technique, in an attempt to verify these findings in man. The results will be published elsewhere.[9]

The method does appear to be valid in the differential diagnosis of renal and extrarenal masses. It would be expected that avascular tumors and cysts would not become opacified, whereas the normal kidney and perhaps vascular tumors would opacify. Studies on the clinical application of this technique are in progress and will be reported separately.

SUMMARY AND CONCLUSIONS

1. A method is described by which contrast visualization of the kidney parenchyma is obtained following intravenous administration of diodrast.

2. The method appears to be of value in physiologic studies on the renal circulation and in the differential diagnosis of renal and extrarenal masses.

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TREATMENT OF TUMORS OF THE THYROID WITH DIVIDED DOSES OF RADIOACTIVE IODINE*

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RADIOAUTOGRAPHS of nodular goiters and of carcinomas of the thyroid usually show a very spotty and irregular take-up of I^{131} (Fig. 1). Because most of the I^{131} may be taken up in a few very active but very small areas and because the beta radiation of I^{131} penetrates the tissues only for a distance of 1 or 2 mm., the greater part of the tumor may receive little or no radiation. If adenomas or carcinomas of the thyroid are to be treated successfully with I^{131}, it is necessary to change the functional activity of the tumors so that all parts of them, or at least all parts that it is desirable to destroy or inactivate, take up I^{131}.

Rawson[1] has attempted to solve this problem in metastatic carcinoma of the thyroid by removing the thyroid and by giving thiouracil and thyrotropic hormone. He has succeeded, in some cases, in producing significant increases in the total take-up of I^{131}. Although the total uptake of these tumors may be increased, it is not clear whether the uptake following these measures is uniform, or whether various parts of the tumor continue to take up I^{131} unequally. Judging from our experience with multinodular goiters treated with propyl thiouracil before administration of I^{131}, I believe that it is quite likely that the take-up is still irregular and that large areas still remain untreated even after the administration of large doses of I^{131}.

Rawson *et al.*, after preparing patients with thiouracil and thyrotropic hormone, have given very large doses of I^{131} ranging up to 100 mc. In some cases this has caused reactions resembling radiation sickness. It is difficult to evaluate the results of therapy, because sufficient time has not elapsed to determine whether or not the apparent improvement will be permanent.

Since carcinomas of the thyroid tend to take up I^{131} in the same irregular fashion as multinodular goiters the study of the response of nodular goiters to treatment with I^{131} is of interest. Nodular goiters with hyperthyroidism usually require doses of I^{131} three to ten times as large as those which control the hyperthyroidism of Graves' disease and cause the goiter to disappear. Even these doses rarely cause more than a slight diminution in the intensity of the hyperthyroidism or more than a slight diminution in the size of the thyroid unless the I^{131} is given in divided doses. The reason for this is obvious, if one remembers the irregular distribution of tracer doses of I^{131} in radioautographs of nodular goiters, and assumes that all or almost all of the infinitesimally small amount of I^{131} (7 mc. of I^{131} contains iodine equivalent to about 1/50,000 of a minim of Lugol's solution) is taken up by the few small active areas. To increase the dose merely wastes the I^{131} and subjects the patient to unnecessarily heavy irradiation without causing any significant increase in the uptake of I^{131} in the major portion of the thyroid. Although it may destroy the most active areas more promptly and completely than smaller doses, it does not extend its effect to the less active areas which do not take it up.

The uptake of I^{131} by papillary carcinomas of the thyroid is just as irregular as that of multinodular goiters (Fig. 1). This finding could be anticipated from the histopathology of these tumors which varies greatly in different parts of the same tumor and its metastases. Therefore it is reasonable to expect that papillary carcinomas, or any carcinomas which take up I^{131} in an irregular fashion, would fail to regress

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satisfactorily after single doses of I^{131} no matter how large they were. The few active areas would be destroyed faster than with smaller doses but they would not be killed any deader nor would the inactive areas receive significantly larger amounts of radiation.

Our experience with the treatment of a group of 30 patients with nodular goiter

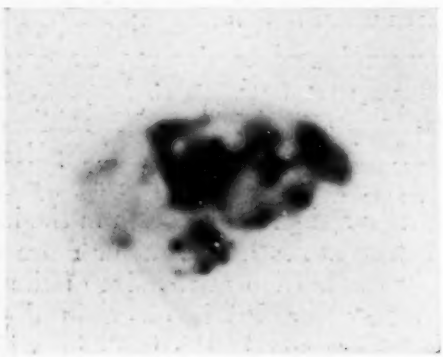

Fig. 1. Radioautograph of lateral cervical metastases of a papillary carcinoma of the thyroid.

with hyperthyroidism by I^{131} has shown that the goiters have almost invariably diminished to from one-third to two-thirds in size after control of the hyperthyroidism. In no case has the goiter disappeared completely as do the diffuse goiters of Graves' disease. In an occasional case there is no significant decrease in the size of a nodular goiter even after the hyperthyroidism is completely controlled. The control of the hyperthyroidism and the diminution in the size of the goiter appear to depend (within certain limits) more upon the number of doses given than upon the size of the individual doses. Even when doses up to 35 mc. have been given in single treatments to patients with nodular goiters, hyperthyroidism has not been controlled although doses as small as 5 mc. have induced myxedema in patients with Graves' disease.

Most papillary carcinomas of the thyroid are operable and do not require treatment with I^{131}, and most of the other malignant tumors of the thyroid, except for the rare angio-invasive adenomas, do not take up I^{131}. Although we have attempted to modify the behavior of some of the more differentiated non-papillary adenocarcinomas by destroying the thyroid with I^{131}, we have not as yet succeeded in causing any of these tumors to take up I^{131}. Our experience is hence limited to the study of 9 patients with papillary carcinomas who were given tracer doses of I^{131} before operation. Radioautographs of the specimens removed showed that only 2 of the 9 papillary carcinomas took up significant amounts of I^{131}. One patient whose tumor took up I^{131} had previously been subjected to a nearly complete thyroidectomy and the radioautograph showed an irregular and spotty uptake of I^{131} in the metastases of the tumor (Fig. 1). Since the primary tumor had been removed and its metastases appeared to be removed completely at the second operation there was no indication for further treatment.

The slow but steady regression of a papillary carcinoma in response to repeated moderate sized doses of I^{131} is outlined in the following report.

Report of a Papillary Carcinoma of the Thyroid Satisfactorily Treated with I^{131}

Case 1. The patient was a man aged twenty-two when first seen at the Cleveland Clinic in 1938 complaining of constipation and acne. The thyroid was described as being palpable but not significantly enlarged.

He was seen intermittently at the Clinic for the next five years and then re-entered complaining of a goiter, which he had first noticed a year before. Examination showed a firm enlargement of both lobes of the thyroid. The surgical consultant noted that the thyroid was extremely hard and that there was a nodule palpable in the posterior triangle of the neck separate from the thyroid. A diagnosis of carcinoma of the thyroid with metastasis was made. Roentgenograms of the chest showed some fibrosis at the hilus and in the lower lobes.

The thyroid and lateral cervical region was explored by Dr. Dinsmore on October 8, 1943, at which time a supraclavicular node was removed and a biopsy was taken from the thyroid. The thyroid tumor had invaded the sur-

rounding tissues and was considered to be inoperable. Sections of the tumor showed infiltration of the thyroid by a papilliferous tumor and the same type of carcinoma was present in the lateral cervical lymph node.

After operation a course of intensive roentgen therapy was given to the thyroid area. There was no primary regression of the tumor in response to the roentgen therapy and within a year additional nodules appeared in the right cervical region. The patient's general physical condition remained good, in spite of the fact that roentgenograms of the chest showed progressive changes which were interpreted as fibrosis of a nodular interstitial type, suggestive of silicosis. The patient had had no exposure to silicosis. By November, 1944, roentgenograms of the chest showed extensive nodular infiltration interpreted as metastatic malignancy with involvement of both lower lobes of the lung. In spite of this the patient remained well clinically and there was little enlargement of the thyroid tumor or its metastasis in the neck.

In January, 1947, inasmuch as the tumor had not enlarged significantly, it was thought that it must be a very low degree of malignancy and a second attempt was made to remove it. The tumor had infiltrated muscle and surrounding tissue, rendering thyroidectomy extremely difficult. It also extended down into the mediastinum and behind the trachea. It was not possible to remove all of the tumor. Again the pathologist reported a papillary carcinoma of the thyroid (Fig. 2).

On September 24, 1947, the patient was given a tracer dose of radioactive iodine and sixteen hours afterward a good concentration of radiation was noted over the lower lung fields, as well as over the thyroid and lateral cervical masses. At that time the lymph node in the right cervical region was estimated to be 2 cm. in diameter, and considerable induration was still palpable in the lower neck on the left.

During the next eighteen months the patient was given a total of 335 mc. of I^{131} in eight doses. The basal metabolic rate before treatment was minus 3 per cent and remained within normal limits. During this time the thyroid, lateral cervical metastasis, and the metastases in the lungs continued to take up I^{131}. The masses in the thyroid and lateral cervical region grew smaller but did not disappear. The roentgenologic appearance of the pulmonary metastases remained unchanged.

An additional 80 mc. of I^{131} was given, making a total of 415 mc., following which the basal metabolic rate fell to minus 24 per cent, the patient developed myxedema, and the thyroid and lateral cervical masses disappeared. The roentgenologic appearance of the lungs remains unchanged but repeated tracer doses of I^{131} given during the ensuing year and a half have shown no uptake in the neck or in the lungs and

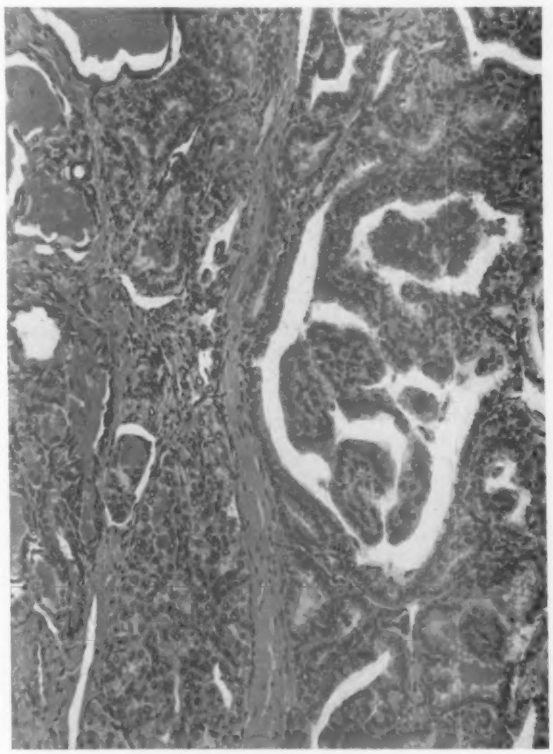

Fig. 2. Case 1. Papillary carcinoma of the thyroid. (×70)

the patient, who is receiving 3 gr. of desiccated thyroid daily, is working and feels entirely well. He develops myxedema when thyroid is withdrawn. It is thought that the roentgenologic findings may be due to fibrosis around the tumor nodules in the lungs.

It is now seven years since the thyroid carcinoma was first noted and no tumor tissue is palpable in the neck.

POSSIBLE DANGERS OF TREATMENT WITH I^{131}

There is reason to believe that I^{131} cannot be given to all patients with carcinoma of the thyroid with impunity. If the normal thyroid function is abolished by thyroidectomy or administration of I^{131}, the pitui-

tary is stimulated to increase its output of thyrotropic hormone. This in turn may stimulate the thyroid tumor to take up I^{131} and may result in its destruction. But if the tumor does not take up I^{131}, the thyrotropic stimulation may cause it to grow more rapidly and hence may shorten the course of the disease. The sequence of events apparently occurred in the following case.

Case II. The patient was a woman, aged sixty-eight, who stated that she had developed shortness of breath, cough, and rapid pulse two and a half years before entry. Roentgenograms of the chest at that time showed extensive pulmonary metastasis of the thyroid carcinoma. An unknown amount of roentgen therapy had been given to the pulmonary metastases without any significant change. She had lost 44 pounds in weight.

Examination showed emaciation, pulse rate of 120, fine tremor, moist skin, and typical evidence of severe hyperthyroidism. The blood pressure was 158/84 and the basal metabolic rate was plus 77 per cent. Blood cholesterol was 114. A hard multinodular goiter was present whose estimated weight was 100 gm. The majority of this tumor was on the right side, only a very small adenoma being palpable on the left. Posterior to the hard fixed right lobe of the thyroid was a separate metastatic nodule 2.5 cm. in diameter. A biopsy taken from the lateral cervical nodule showed a Hürthle cell type of carcinoma. In spite of the fact that a tracer dose of radioactive iodine had been given before the biopsy was taken, the tissue took up no significant amount of radioactive iodine as proved by radioautograph. The uptake of radioactive iodine as measured by a Geiger counter was twice as great on the left side, away from the main tumor, as it was on the right and no I^{131} was taken up by the pulmonary metastases.

It was hoped that after the correction of the hyperthyroidism the thyroid tumor would take up radioactive iodine. Consequently, 24 mc. of I^{131} was given. Two months later the basal metabolic rate had fallen to plus 27 per cent. The patient was given an additional 30 mc. of I^{131} and a month later the basal metabolic rate had fallen to plus 7 per cent, the pulse rate had fallen to 84, and the patient had gained 11 pounds, felt very much better and was no longer short of breath. The tumor still did not appear to take up any radioactive iodine, and therefore an additional 40 mc. was given in an attempt to induce myxedema. At this time the cervical region took up only 30 per cent of the administered dose of radioactive iodine. The thyroid tissue on the left had diminished in size and it was thought that the thyroid tumor on the right was somewhat smaller although this was uncertain.

Despite the administration of radioactive iodine in divided doses for a total of 140 mc. over a period of eight months, it was impossible to reduce the basal metabolic rate below minus 6 per cent. A slight tachycardia persisted, the pulse running between 80 and 90, and yet the patient showed clinical evidence of myxedema. The skin became very dry, the face puffy, and the patient felt better when desiccated thyroid was given in small doses. A slight secondary anemia which had been present since the beginning of treatment persisted, but there was no change in blood calcium or urea.

It was thought that the relatively high basal metabolic rate persisting in the presence of clinical myxedema was a nonspecific result of the extensive metastasis which was present in the chest and this belief was supported by the fact that the uptake of radioactive iodine in the cervical region and over the chest was negligible.

The pulmonary metastases which had remained stationary in size during a period of observation of nearly three years began to enlarge rapidly as soon as clinical evidence of myxedema developed and at the same time the patient began to show symptoms and signs characteristic of extensive malignancy and again began to lose weight after having gained weight up to 21 pounds above her original level.

Nine months after treatment was initiated the patient died, apparently as the result of rapid enlargement of the thyroid tumor and its metastases.

The fact that the patient's tumor did not enlarge for nearly three years while the hyperthyroidism was present, and the fact that it enlarged rapidly and the patient's general condition deteriorated rapidly after myxedema was induced, suggest the possibility that the growth of the tumor was stimulated by thyrotropic hormone, the production of which had been inhibited while the hyperthyroidism was present. Since the tumor could not function and take up radioactive iodine, the net result of

treatment was stimulation rather than inhibition of the growth of the tumor.

DISCUSSION

Our experience indicates that if treatments are given intermittently at intervals of six to eight weeks over a long enough period of time all functioning tumor tissue ultimately can be destroyed without requiring the administration of an excessively large amount of I^{131} at any one time. Unfortunately, in the case of carcinoma of the thyroid, it is the more undifferentiated portions of the tumor which not only may be the most dangerous, but which do not take up I^{131}. It remains to be seen whether these areas will survive and ultimately cause uncontrollable recurrence of the tumor or whether they will all be transformed, in response to the body's needs, to functioning tissue capable of being destroyed by I^{131}. It is already established[1] that ablation of the normal thyroid by operation or I^{131} causes at least part of certain malignant tumors to take on the function of the normal thyroid and it is hoped that all areas of these tumors eventually can be rendered functional and destroyed.

In cases in which the tumor cannot be made to take up I^{131}, serious consideration should be given to the possibility that thyrotropic stimulation resulting from the myxedema might cause increased growth activity of the tumor This complication could be avoided by the administration of desiccated thyroid in doses of 3 gm. or more daily.

SUMMARY

1. Multinodular goiters may regress in size and associated hyperthyroidism can be controlled by administration of multiple doses of I^{131} given at intervals of six to eight weeks.

2. Multiple smaller doses of I^{131} appear to diminish the size of nodular goiters and control hyperthyroidism more satisfactorily than single large doses.

3. Since I^{131} is taken up irregularly by nodular goiters, most of a given dose, regardless of its size, may be concentrated in small actively functioning areas.

4. Large areas which are not functioning actively may receive little or no radiation from a single dose of I^{131}.

5. After the most active areas are destroyed or inactivated by a small dose of I^{131} it appears that the less active areas can in turn be inactivated or destroyed by subsequent small doses.

6. Papillary carcinomas of the thyroid tend to take up I^{131} in an irregular manner similar to nodular goiters.

7. A case of papillary carcinoma of the thyroid in which the primary tumor and its cervical metastases have disappeared in response to multiple doses of I^{131} is reported.

8. It is suggested that tumors of the thyroid which take up I^{131} in an irregular manner are more effectively and safely treated by divided doses of I^{131}, given at six to eight week intervals, than by single massive doses.

9. If a thyroid tumor does not take up I^{131}, the induction of myxedema may stimulate growth of the tumor.

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THE THEORY AND METHODS OF THE RADIOAUTOGRAPHIC LOCALIZATION OF RADIOELEMENTS IN TISSUES

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RADIOAUTOGRAPHY is a method for detecting radioisotopes, based on their ability to affect the silver bromide crystals of photographic emulsions. Such crystals act as microdetectors of radiation and are therefore useful in visualizing locations of radioelements in the microscopic structures of the body. Practically, a radioautograph is obtained by placing a tissue section in contact with photographic emulsion, allowing sufficient time for exposure, and then developing as in ordinary photography. The resultant radioautograph consists of accumulations of black silver granules overlying those areas in the tissue section which contain the radioactive material (Fig. 1); and, by comparing the photographic image with the tissue section, such areas of activity can be fairly accurately assigned to definite microscopical structures.

The present work deals with the theoretical concepts involved in radioautography, as well as with the technical details required for satisfactory results. In addition, while the applications of radioautography to biology and medicine have been reviewed previously,[4,35,41,42,49,87,98] recent radioautographic results will be presented to illustrate the possibilities of the method.

One of the most productive uses of radioautography has been to follow the movement of a labeled substance through the various parts of an organ (as shown below in the case of the thyroid and bone). Similarly, the site of synthesis or degradation of a labeled substance may be revealed by radioautographs. The possibilities imply that the tissue components responsible for the radioautographic reactions are chemically characterized—a frequently overlooked requirement for this type of work.

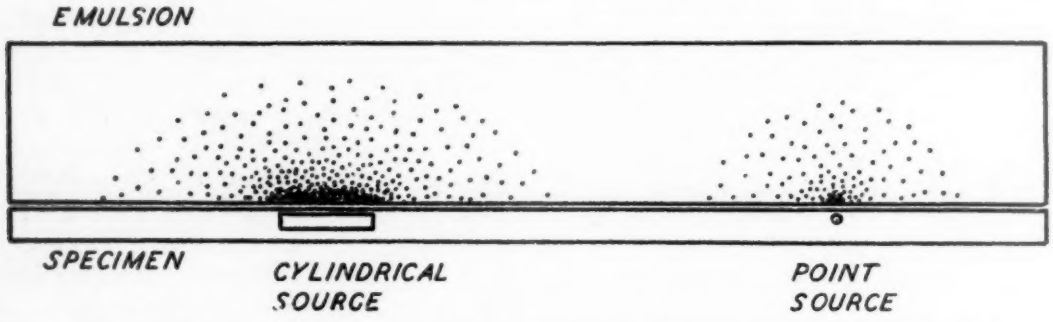


FIG. 1. Diagrammatic representation of the effect of a photographic emulsion (above) of a point source of radioactivity (right hand side of specimen), and a cylindrical source of radioactivity (left hand side of specimen).

As with other methods involving the use of radioisotopes, it is assumed that the chemical behavior of a labeled substance is identical with that of its stable counterpart. This will also be true of the biological behavior, provided (1) the amount of radioactivity administered be small enough not to have a significant radiochemical effect, and (2) the amount or weight of material injected be sufficiently small not to produce a significant increase in the amount of this substance present in the circulation. The

labeled substance will then truly act as a "tracer" of the normal metabolism. Often, especially in the case of isotopes prepared by transmutation, the weight is so small that it cannot be estimated by chemical or spectroscopic means; such a "tracer" dose is called "carrier-free."

So far, only a few of the available radioelements have been used for radioautographic studies. Those with a short half-life (minutes to hours) are usually not suitable, since, after the delays of histological processing, the tissue sections no longer contain sufficient radioactivity for radioautography. The shortest half-lives that proved usable are twelve hours in the case of I^{130}, and fourteen hours in the case of Na^{24}. On the other hand, long-lived isotopes, such as the 5,500-year C^{14}, must contain many more atoms of isotope per millicurie than short-lived elements, and therefore cannot be prepared as carrier-free material. As a result, these radioelements are often less suitable for tracer experiments. Isotopes with intermediate half-lives can usually be prepared carrier-free, in addition to affording sufficient time for the handling and exposure of the preparations. They are therefore the ones most commonly used, e.g. the eight-day I^{131}, the fourteen-day P^{32}, the thirty-five-day Sr^{89}, etc.

THEORETICAL BASIS OF RADIOAUTOGRAPHY

While the basic theory of radioautography is quite simple, its application to the fine localization of radioelements in tissues introduces somewhat more complex theoretical considerations. In the radioautograph, an increased density of silver granules occurs in the emulsion over the sites of radioactivity. Localization implies that we can accurately associate these areas of increased density with tissue structures, and, as a corollary, that we can distinguish between areas of increased density closely adjacent to one another. The closer such areas can be and still be distinguishable, the better is said to be the resolution of the method. Both resolution and density will depend on:

(a) The geometrical relationship of the radioactive source and the overlying emulsion.
(b) The energy and intensity of the radiation.
(c) The characteristics of the photographic emulsion.

The theoretical discussion will examine these factors in an attempt to help formulate the conditions for obtaining the most satisfactory radioautographic results. Since the radioautographic action of α-emitters has been thoroughly studied[25,52,98] and that of γ-radiations is practically negligible, the discussion will deal specifically with the radioautography of β-emitters.

1. *The Geometrical Relations of Source and Emulsion.* The radioautographic preparation consists of the section, the overlying emulsion, and the space between the two, i.e. the interspace (Fig. 1, 2, 3). Any variation in the geometrical arrangement of these components, such as variations in their respective thicknesses, will affect the sharpness and density of the photographic image obtained. In order to analyze these effects, Pelc[28] assumed that the specimen contained a site of radioactivity concentrated into a point (P) (i.e. a point source), as in the diagrammatic model in Figure 3. The intensity of the source resulted, over a given period of exposure, in an amount of radiation designated by the symbol $\mathcal{Q}$ (often referred to as "exposure"). Now, since the intensity of the radiation at any point S in the emulsion is inversely proportional to the square of the distance from P (i.e. r), then the amount of radiation received at this point can be expressed as $\mathcal{Q}/r^2$. It is tentatively assumed that the blackening at point S is proportional to this amount of radiation, i.e. $A\mathcal{Q}/r^2$, where A is the sensitivity of the emulsion. This may be calculated for any element δx along a line through S perpendicular to the plane of the

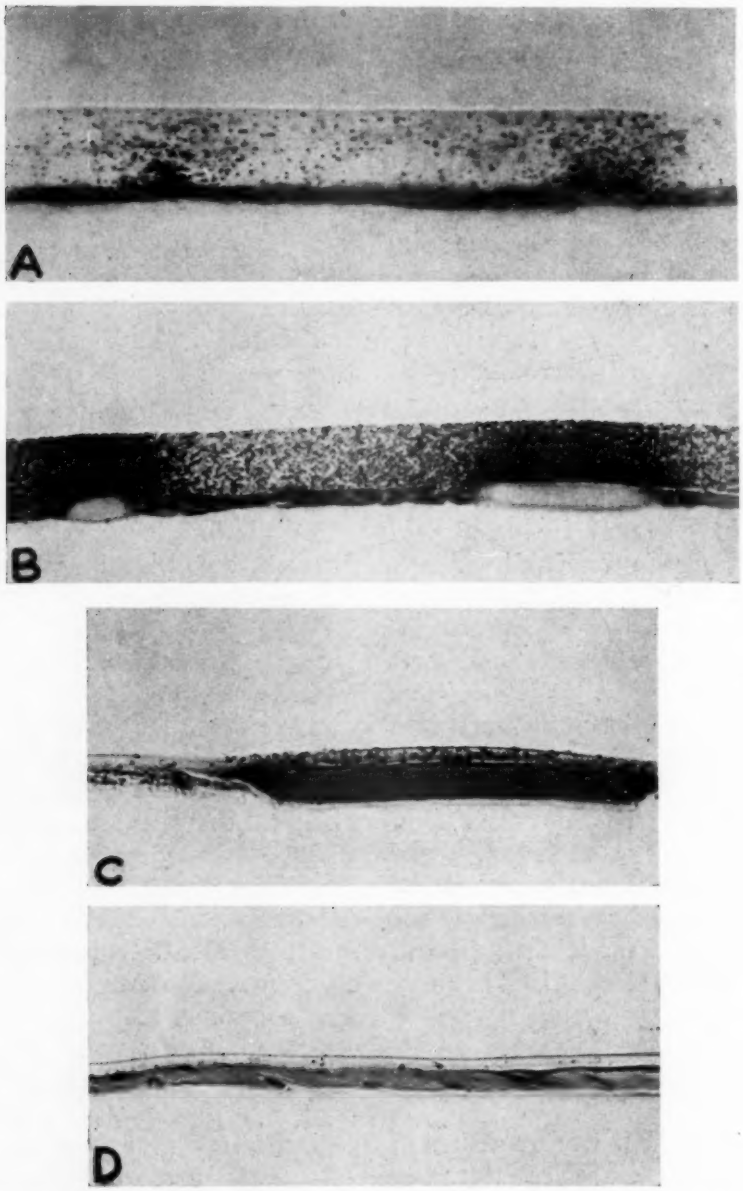


FIG. 2. Profile sections of "coated" radioautographs. Sections of rat thyroid containing radioiodine were mounted on strips of acetate film, instead of glass slides, and coated with photographic emulsion, as described in the text (page 435). After exposure the preparations were developed and fixed to obtain the radioautographic image, then treated with chromalum to harden the emulsion, embedded in paraffin and sectioned. ×450. The emulsion (upper layer) and section (lower layer) are very close together, *i.e.* the interspace between them is very small.

(*A*) A cross section of a radioautograph coated with E.K. medium lantern slide emulsion and optimally exposed. Two areas of thyroid colloid containing radioactivity are present in the section. Note how the radioautographic reaction is most dense in the region of the emulsion closely adjacent to the radioactive source. In between the two sources, the emulsion shows a scattering of silver granules which constitutes background fog.

(*B*) A similar preparation to that shown in (*A*), coated with Ilford halftone stripping film. In this case, however, the radioautograph has been overexposed. Note the increased spread of the photographic image as well as a marked increase in the background fog.

(*C*) A cross section of a radioautograph coated with a diluted E.K. medium lantern slide emulsion (see

emulsion. The sum of these densities[1*] will represent the density ${}^{P}D'$ visible through the microscope at a distance (y) from the perpendicular through the point source P. The maximum density (${}^{P}D'_{max}$) will occur along the line PR passing through the point source P. By calculating the values of ${}^{P}D'$ in arbitrary units for various distances (y) from the line PR, it is possible to construct a curve showing a profile of the densities produced by the point source at various points in the photographic emulsion. Curves of this type are given in Figures 4 and 5, and have been constructed for conditions in which the point source is at various distances from the edge of the emulsion (i.e. distance p is varied). It is evident that the maximum density (${}^{P}D'_{max}$) is greatest when the source is closest to the emulsion.

As an arbitrary measure of resolution, Pelc[28] has suggested that the dispersion of the curve at the point where the density is half the maximum density be used. This distance is indicated by the dashed lines on the graphs and is expressed in microns (μ) in the tables. The smaller this distance, the better is the resolution, that is, the sharper the image will be. And from the curves in Figures 4 and 5 it may be seen that the best resolution is obtained when the source is closest to the edge of the emulsion. This is indicated more clearly in Figure 6 which shows the variation of resolution with variation in source-emulsion distance for various thicknesses of emulsion. It is further evident that, within the range of values cited, variation in the emulsion thickness has relatively little effect on the resolution of the images produced by a point source as compared to the effect of the distance between the source and the edge of the emulsion. In a radioautographic preparation the maximum value for this distance is equal to the thickness of the section and the width of the interspace. Thus, in the theoretical case, the reduction of the section thickness and the interspace to a minimum will give the finest resolution.

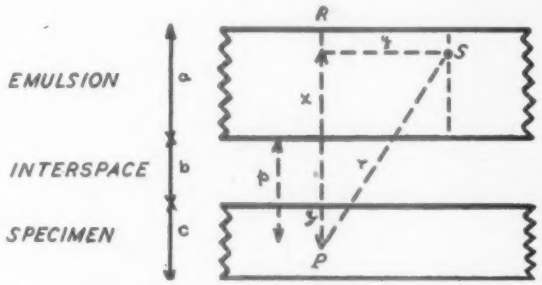


Fig. 3. Schematic representation of the action of a radioactive point source, P, on a photographic emulsion. P is a point source of radioactivity in the specimen; S is any point in the emulsion; a = thickness of the emulsion; b = interspace between specimen and emulsion; c = thickness of specimen; PR is a perpendicular through P, assuming that edges of specimen and emulsion are parallel to one another; x, y, z = as indicated by dotted lines; r = distance PS; $p = z + b$, i.e. distance of point source P from edge of the emulsion (adapted from Pelc[28]).

In practice, the radioactivity source in the tissue section is arranged as an irregular geometrical solid often approximating a plane (as in the shaft of the bone), or a cylinder (as in the thyroid colloid). In order to obtain some idea of the factors

[1*] This summation may be obtained by integrating the densities along the perpendicular through S to obtain ${}^{P}D$.

$$ {}^{P}D = \frac{A\mathcal{Q}}{y}\tan^{-1}\frac{ay}{y^2+p(p+a)} = A\mathcal{Q}\,{}^{P}D' \text{ when } y>0 $$

and the maximum density ${}^{P}D_{max}$ may be obtained:

$$ {}^{P}D_{max} = A\mathcal{Q}\frac{a}{p(p+a)} = A\mathcal{Q}\,{}^{P}D'_{max} \text{ when } y=0, $$

${}^{P}D'$ and ${}^{P}D'_{max}$ being used when $A\mathcal{Q}$ is kept constant.

text, page 435), optimally exposed as in (*A*). An area of radioactive thyroid colloid is visible. Note how closely the radioautographic image corresponds to the radioactive source and how little interference there is from background fog. The reduction in fog is more apparent in (*D*), which is another area from the same preparation in which the tissue is not radioactive. Note how only a few scattered fog granules are visible in the emulsion layer.

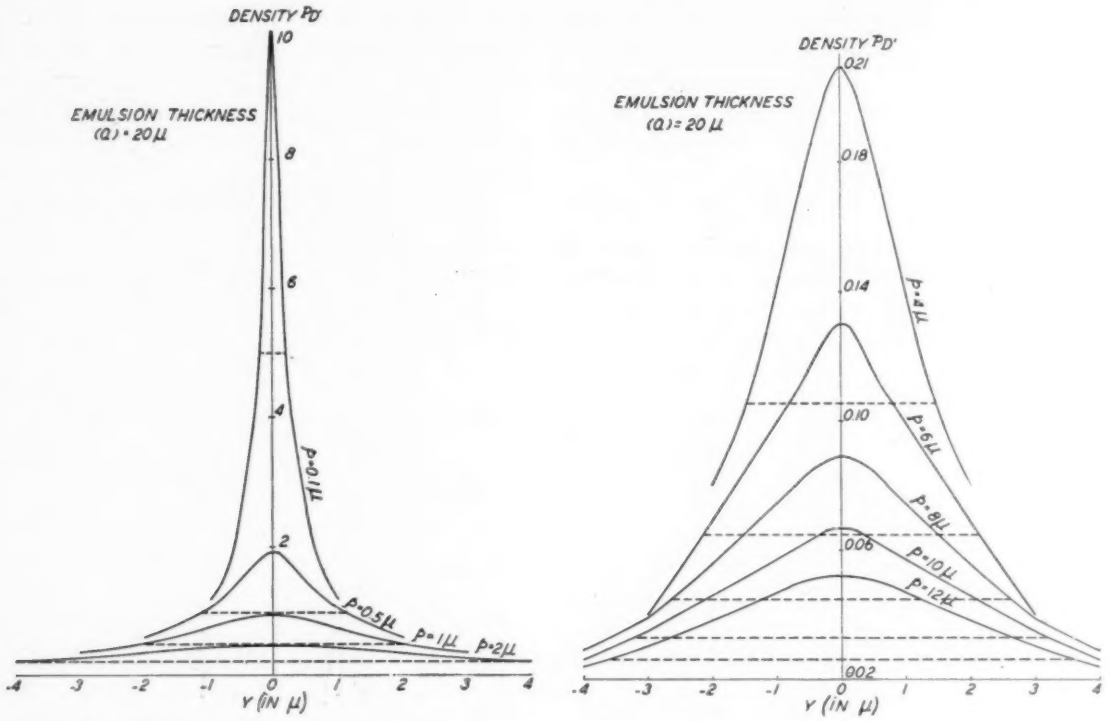
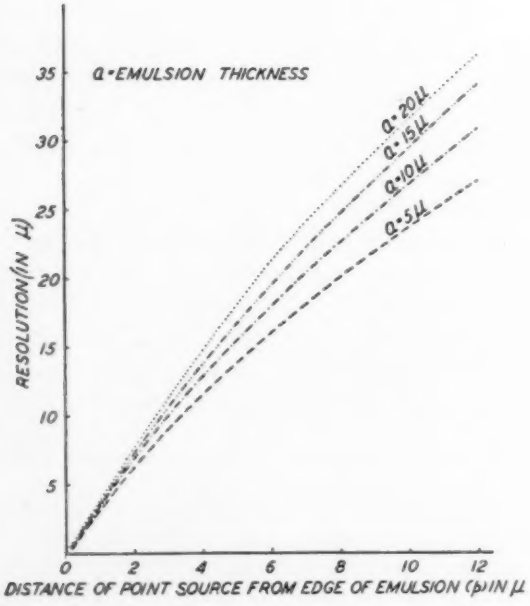


FIG. 4 and 5. Influence of interspace on resolution and photographic density ($^{P}D'$) of the radioautographic image resulting from a point source of radioactivity. A series of characteristic curves showing the density in arbitrary units at various distances y in the emulsion from the perpendicular through point source (see Fig. 3), for various point sources at distances, p, from the edge of the emulsion. The dotted lines measure the resolution. These curves illustrate how the decrease in the distance p increases the maximum density and improves the resolution obtainable with a point source, when the emulsion thickness is 20 μ.



affecting density and resolution under these conditions, it is necessary to expand the theoretical treatment of the point source to cover the effects of line, plane and cylindrical sources.

Curves similar to those shown in Figures 4 and 5 were calculated for the line source[2*]

[2*] Using a line source perpendicular to the section (Fig. 3), it is assumed that the intensity of the source is uniform along the line, and is equal to ^{L}Q per unit length. Under these condi-

FIG. 6. Influence of emulsion thickness on the resolution of a point source radioautograph. Curves illustrating the relation between resolution and distance, p, of a point source from edge of emulsion for various emulsion thicknesses. It is concluded that the emulsion thickness is of relatively minor significance compared with the distance p.

and gave the information found in Table I. From these data it may be seen again that decreasing the interspace produces the most significant improvement in resolution and the greatest increase in maximum density.

By integrating the characteristic curves of a line source, it was possible to determine the radioautographic effect of a plane source.[3*] For a plane 40 microns in length, the density over the middle of the plane is about twice that over the ends. Similarly, the resolution is best over the middle and is improved by a decrease in the widths of interspace, specimen and emulsion.

The data obtained with the plane source may now be used in the graphical analysis of the photographic blackening produced by a cylindrical source.[4*] For a cylinder of

Table I

THE RESOLUTION AND DENSITIES RESULTING FROM A "LINEAR SOURCE" OF RADIOACTIVITY UNDER VARIOUS CONDITIONS OF SECTION, EMULSION, AND INTERSPACE THICKNESS

Emulsion Thickness	Interspace	Section Thickness	Resolution	Max. Density
(μ)	(μ)	(μ)	(μ)	
5	0.1	5	2.3	3.2
5	0.1	10	2.8	3.5
10	0.1	5	2.7	3.5
10	0.1	10	3.7	3.9
15	0.1	5	3.3	3.7
15	0.1	10	4.4	4.1
5	0.5	5	5.7	1.8

tions, the maximum density ($^{L}D_{max}$) may be determined from the expression:

$$^{L}D_{max} = A^{L}Q \log \frac{(b+c)(b+a)}{b(b+c+a)} \qquad \text{i.e., } y=0$$

or if $A^{L}Q$ is kept constant, $^{L}D_{max} = A^{L}Q\,{}^{L}D'_{max}$.

For other values of y, $^{P}D'$ vs. p is plotted over the limits $p=b$, $p=b+c$ (see Fig. 3 for an explanation of symbols), and the densities $^{L}D'$ are found by graphical integration for a particular a. Analogous values have been determined by Pelc using a somewhat different mathematical manipulation.

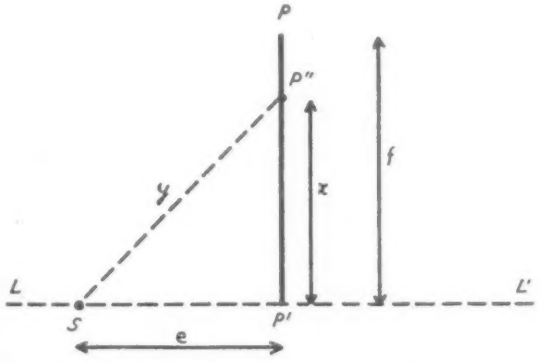


Fig. F. 1. Plan view of emulsion with PP' the projection on the emulsion of the radioactive plane source of length f, present in the histological section. LL' is any line in the emulsion perpendicular to the projection of the source. S is any point on LL'.

[3*] Assuming a plane source (Fig. F.1) of uniform radioactive intensity ^{PL}Q per unit area, for a particular emulsion thickness, a, the photographic density at S for any distance e, is:

$$^{PL}D = A^{PL}Q \int_{x=0}^{x=f} {}^{L}D'dx = A^{PL}Q\,{}^{PL}D'$$

The graph $^{L}D'$ vs. x can be obtained from (1) the expression:

$$x^2 = y^2 - e^2$$

and (2) the curve $^{L}D'$ vs. y for the particular dimensions.

The value of $^{PL}D'$ is then obtained by graphically integrating the curve $^{L}D'$ vs. x over the appropriate interval of x.

[4*] According to the dimensions of the cylinder (Fig. F.2), the lengths f of various planes PP' are calculated; and then the densi-

Table II

THE RESOLUTION OBTAINED WITH "CYLINDRICAL SOURCES" OF RADIOACTIVITY UNDER VARIOUS CONDITIONS OF SECTION, EMULSION, AND INTERSPACE THICKNESS

Emulsion Thickness	Interspace	Section tion Thickness	Resolution	Curve No. (Fig. 7)
(μ)	(μ)	(μ)	(μ)	
5	0.1	2	5.0	I
5	0.1	5	6.0	III
5	0.5	5	6.4	II
10	0.1	5	8.0	IV
20	0.1	5	9.0	V
35	0.1	5	10.2	VI

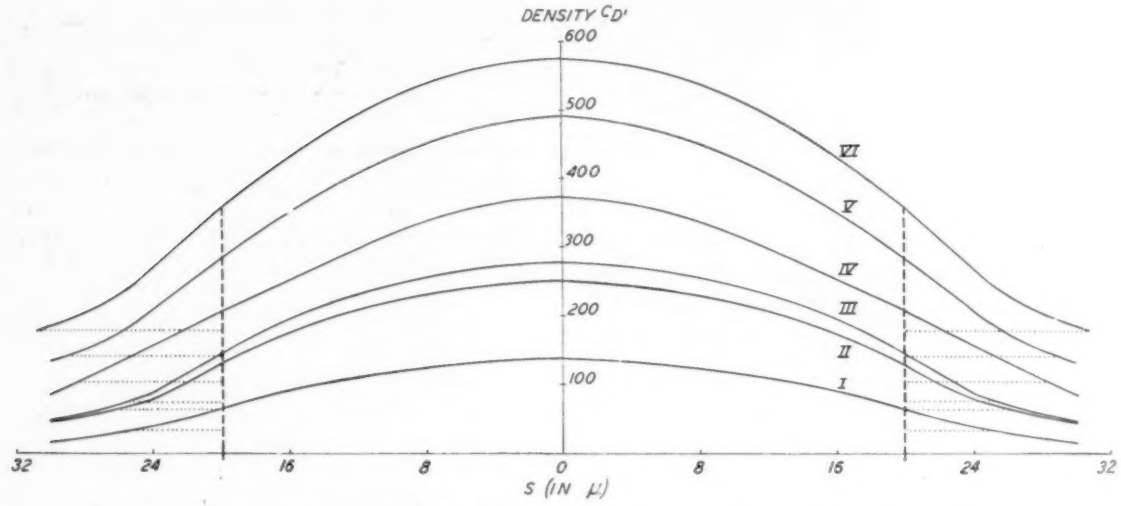


FIG. 7. Geometric factors influencing the radioautograph of a cylindrical source. Curves illustrating the blackening density and distribution, $^{C}D'$, in arbitrary units, at distances, S, from the projected center of a solid circular cylindrical source of 40 μ diameter. The dotted lines measure the resolution. The roman numerals refer to the conditions given in Table II.

radius 20 μ the blackening in the emulsion is distributed according to the curves shown in Figure 7. Resolution was arbitrarily redefined as twice the distance from the edge of the source projected onto the emulsion to the point on the curve whose density was one-half that found over the edge of the source. This distance is indicated by the dotted lines on each curve, and the results obtained are shown in Table II.

It may be seen that the best theoretical resolutions for a source of this size are not as good as for the smaller sources (Table I, Fig. 6). On the other hand, variations in emulsion, section and interspace have a relatively smaller effect on resolution.

In practice most sources will be considerably smaller in size than the cylinder considered and will often approximate a linear type of arrangement. Theoretically, then, the maximum possible resolution with a 5 μ section, 5 μ emulsion, and 0.1 μ interspace is about 2.3 μ (Table I). Stevens[90] was able to separate two lines 2.5 μ apart using a fine grain emulsion. On the basis of these theoretical and practical findings, we have adopted in this laboratory a radioautographic preparation which consists of a 5 μ section and a 5 to 15 μ emulsion, and which is prepared by methods giving a negligible interspace (the mounting, coating and stripping techniques, as described below). Sample preparations of the coated type are shown in profile in Fig. 2.

2. *The Intensity and Energy of the Radi-*

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ty for the entire solid is determined at a point at a distance u from the edge of the circle, by the graphical integration of:

$$^{C}D = A^{C}\mathcal{Q} \int_{e=u}^{e=u+2R} 2\,^{PL}D'\,de = A^{C}\mathcal{Q}\,^{C}D'$$

assuming a uniform radioactive intensity, $^{C}\mathcal{Q}$, per unit volume. The value $^{C}D'$ is then obtained by graphical integration of the appropriate curve, $^{PL}D'$ vs. e.

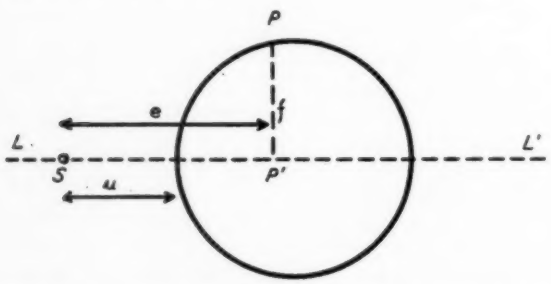


FIG. F. 2. Plan view of emulsion with a circle being the projection on the emulsion of the radioactive, solid cylinder of radius R present in the histological section. LL' is a line in the emulsion perpendicular to the projection of the source. S is any point on LL'.

ation. In evaluating the geometrical factors, the amount of the radiation (Q) was kept constant and the effects of the β-particles on the emulsion were assumed to be uniform. It is necessary now to examine the effect of variations in the amount and spectrum of the radiation on the radioautographic image. This will first require an understanding of the manner in which β-particles affect a photographic emulsion.

(a) The mechanism of photographic action. Photographic emulsions in general consist of silver bromide crystals, or "grains," embedded in gelatin; the bromide concentration and mean diameter of the crystals varying with the different types of emulsion (Fig. 8). The crystals may also contain impurities, such as silver sulfide which play an important role in the photographic process.

When the emulsion grain is exposed to radiant energy, such as white light, there is an excitation and release of electrons from some of the bromide ions. These electrons are, however, trapped within the crystal at specific irregularities, such as are provided by the specks of silver sulfide. Subsequently, silver ions in interstitial positions are attracted to these points, known as "development centers," and are electrically neutralized. This results in the deposition of metallic silver, the so-called "photolytic silver" which forms the "latent" image. If sufficient photolytic silver is deposited in the grain it becomes developable, that is, the developer (a reducing solution) converts silver ions to metallic silver which then precipitates around the development centers, and thus makes the crystals visible as black granules. A complete description of this process may be found in Mees[66] and James and Kornfeld.[51]

The photographic mechanism in the case of radioactive emanations is similar to that described for radiant energy, except for the first stage. When a radioactive particle passes through a grain it will, by direct collisions, release orbital electrons which will then migrate to the sensitivity specks.

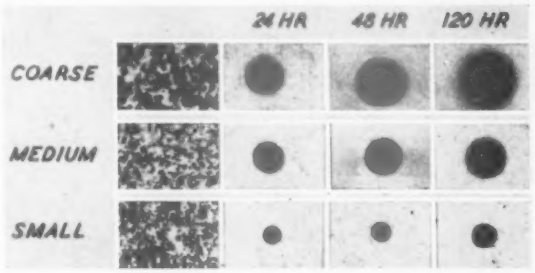


Fig. 8. Influence of the size of the grain and length of exposure on the size of the radioautographic image (composite figure made from Boyd[14]). The source consisted of radiorubidium which acted on three kinds of emulsions, identified by the size of their grains (left hand side) for 24, 48 or 120 hours. The size of the image increased with the size of the grain, as shown by comparisons of the pictures along vertical lines, and with the length of exposure, as shown by comparing pictures along horizontal lines. Therefore, resolution is improved by decreasing the size of the grain or decreasing the exposure.

The efficiency of the release of these electrons will depend on the energy of the β-particles.

(b) The energy of the radiation: the β-ray spectrum. The assumption previously made, that the effect of each β-particle on the emulsion is uniform, is only an approximation. The photographic action of these particles is a function of their energy which decreases as they travel farther from their source.

Throughout its path, a β-particle loses energy by ionization and radiation (loss of photons), but the rate of these energy losses varies with the initial energy of the particle, as well as with the medium through which it moves. According to a formula arrived at by Bethe, Bloch, and others,[80] it has been possible to derive a relation between the rate of energy loss per unit length of path (space rate of energy loss) for a single β-particle in a medium of silver bromide (Fig. 9). If the assumption is made that this energy loss is contributed to the formation of the latent image, it follows that the photographic efficiency is increased with decrease of energy of the β-particle.[5*]

[5*] It is possible to estimate the photographic efficiency of β-

As the β-particle progresses and loses energy, up to some limit, its photographic efficiency must therefore increase, a fact which has been indicated experimentally by the increasing granule densities toward the ends of C^{14} β-particle tracks.[18] Accordingly, the distribution of blackening, as shown in Figures 4, 5 and 7, should be modified so that the density is greater at the lateral margins of the theoretical curves. This factor will have an adverse effect on the resolution, especially with higher energy rays, for which the rate of decrease of energy and the corresponding increase in photographic activity is initially less. Thus, the photographic action of P^{32} will be increased farther from the source than in the case of I^{131} (most of the β-particles of I^{131} having a lower energy than those of P^{32} (Fig. 10)[30,86] and, therefore, a P^{32} radioautograph will be more diffuse than one due to I^{131}. This fact has been consistently observed throughout the work of the authors.

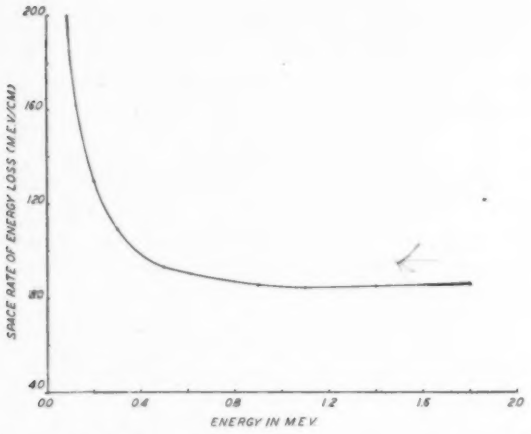


FIG. 9. Relation giving the energy spent per unit distance of path in AgBr by a β-particle with a given energy value. It is observed that the space rate of energy loss increases with decrease in energy of the particle.

The greater spread of the images resulting from the higher energy rays is also due to their greater range. Thus, the maximum emulsion range for C^{14} particles is about 20 μ; for I^{131}, 200 μ; and for P^{32}, 1,400 μ; and therefore the possibilities of diffusion of the image are smallest for the lowest energy isotopes. It may be noted, however, that the effective range is less than the theoretical values cited, since the β-particles undergo some scattering and, in practice, the spread is considerably reduced by limiting the exposure (see below).

(c) THE AMOUNT OF RADIATION (EXPOSURE). In addition to the quality of the radiation, its quantity can be shown to have a marked effect on the resolution of the radioautographic image. The quantity of radiation impinging on the emulsion will depend on the length of time the radioautographic preparation is exposed (i.e. exposure time). The density curves shown in Figures 4, 5 and 7 were constructed on the basis that the density D is directly proportional to the amount of radiation (as indicated by the formula $D=A\mathcal{Q}D'$). This relation is only true up to moderate densities; otherwise, as less grains become available for development, there is a lowered statistical probability of β-particles striking unexposed grains. Accordingly, with further increase in exposure there is less increase

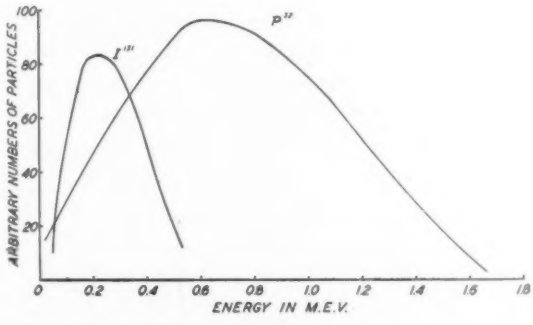


FIG. 10. β-ray spectra for I^{131} and P^{32}. The curves illustrate the relative number of β-particles with given energy.

particles; i.e., the average number of impacts to render a grain developable. As an example, the action of β-radiation from I^{131} on E.K. medium lantern slide emulsion was calculated. Using the mean space rate of energy loss of I^{131} β-particles of AgBr (estimated from calculations involving Fig. 9 and 10), and the average grain size, the mean energy expended per grain was evaluated assuming statistical variations in the direction of the particles. The photochemical effect of Ag atom deposition was compared with that of photons of equivalent energy.[45,51]

It was found that 5–10 β-particle impacts are required to render a grain developable on the basis of interpretation of the number of photolytic silver atoms deposited.[97] This estimate is comparable with that found in the literature.[49] The details of these calculations will be published elsewhere.

in the density.[6*] In the radioautographic image, this effect will be greatest in the region of maximum density and will result in a flattening of the characteristic curves (Fig. 4, 5, and 7). The resolution should then be considerably poorer than that indicated in the curves. This indicates that *low exposure of the radioautographic preparation is required for optimal resolution of the photographic image.*

The practical importance of this requirement was emphasized previously on the basis of empirical observations[57] and is demonstrated experimentally by pictures *A* and *B* of Figure 2. There is a greater spread of the density in the preparation *B* allowed to expose the longer time period. It may be seen that this increased exposure has also resulted in an increased fogging of the emulsion over the non-radioactive areas of tissue. This same phenomenon has been demonstrated macroscopically by Boyd[14] whose results are shown in Figure 8, from which it may be seen that the diameter of the image increases with increasing length of exposure. This increase in image size will result in poorer resolution.

3. *The Characteristics of the Emulsion.* The final factor to be considered is the role of the emulsion. Most of the data accumulated on the influence of the emulsion characteristics on the photographic image[66] will probably apply to the radioautographic image as well. An attempt will be made to determine the conditions under which the best sensitivity and resolving power are obtained.

(a) Grain size is obviously important. The larger the grain size, the higher is the statistical probability of its being traversed by a β-particle and the greater is the energy absorbed. Accordingly, the larger the grain, the more silver atoms are reduced for the same amount of incident radiation. Thus an increase in grain size results in an increased sensitivity of the emulsion. This increase is, however, accompanied by a decrease in resolving power, as demonstrated experimentally in Figure 8, from which it may be seen that the fine-grained emulsion gave the most circumscribed image. Thus, from the point of view of localization, the finer-grained emulsions are preferable. The disadvantage of low sensitivity may be overcome to some extent by the addition of sensitizers and, in fact, emulsions of this type (nuclear track emulsions) are being produced commercially (Ilford and Eastman Kodak—hereafter referred to as E.K.—Company).

(b) Grain concentration. The greater the concentration of grains for a given volume of emulsion the greater is the maximum density obtainable. Thus, both Ilford and E.K. nuclear emulsions have a high concentration of silver bromide. In addition, the larger number of grains tends to increase the sensitivity of the emulsion.

(c) Grain uniformity. Broadly speaking, grains of a given size have a tendency to respond in a similar manner. Therefore, emulsions with a uniform grain size will have a high contrast. On the other hand, emulsions with a wide range in grain size will have a low contrast. In order to obtain a good resolution for a given small area, a high contrast is desirable, although it requires an optimum exposure time in order to avoid over-exposure and loss in resolution. For practical purposes, a low contrast may be desirable in routine preparations with many sites of different intensities.

[6*] A formula (Yagoda[98]) relating photographic density and exposure to radiation has been described as

$$D = Dm(1 - e^{-K\mathcal{Q}}),$$

where D is photographic density,
Dm is maximum D possible for the emulsion,
$\mathcal{Q}$ is the amount of radiation or exposure, which is the integrated product of intensity and duration of exposure,
K is a constant.

It is interesting to note that this formula has been found to successfully verify the experimental findings of Marinelli and Hill[64] relating density to exposure to I^{131} and P^{32}.

For low values of $\mathcal{Q}$, this relation reduces to

$$D = Dm \cdot K\mathcal{Q}$$

which was the basis accepted. Otherwise, it is informative to note that

$$1 - e^{-K\mathcal{Q}} < K\mathcal{Q}$$

so that the density as recorded in the characteristic curves (Fig. 4, 5, and 7) is too high.

(d) CONDITIONS OF DEVELOPMENT AND FIXATION. No definite improvement of the resolution has been noted in this laboratory with fine grain developers, but no systematic studies were carried out. In regard to development time, Mees[66] states that, as development progresses, the resolving power rises rapidly to a maximum, drops slightly, and then remains approximately constant. Short developments have been used in this laboratory with good results, provided sufficient time is allowed for the developer to reach the deeper layers of the emulsion. Frequently, there is some reduction in resolving power as the temperature of the developer is raised, and therefore development should be carried out at low temperatures such as 18–20° C.[66]

(e) FOG is the photographic density obtained when unexposed portions of emulsion are developed. Gelatin normally protects silver bromide from reduction unless photolytic silver has been produced; but all emulsions contain some grains that are developable spontaneously. These grains probably contain development centers of increased sensitivity.

The black granules due to spontaneous fog have a greater compactness of silver and a greater solubility in certain chemicals (fog reducers) than those of the image. Attempts to decrease this fog with the so-called contrast-increasing reducer[94] have been made in preliminary experiments here, with some measure of success. However, attempts to produce fog free emulsions, as suggested by Liebermann and Barschall[61] have, in our hands, led to a considerable decrease in the sensitivity of the emulsion, and have been abandoned.

Emulsions which are diluted with water result in a thin coating which retains its original concentration of silver halide and presumably its sensitivity. Since, with moderate exposures, the photographic effect is close to the tissue surface (Fig. 2*A*), while fog granules are distributed uniformly throughout the emulsion, reduction of the emulsion thickness will result in a greater decrease of the fog density than of the image density. This is illustrated by the profiles of dilute emulsion radioautographs shown in Figure 2, *C* and *D*. Fog has been reduced to a few scattered granules in the unexposed portions of the emulsion (Fig. 2*D*) while the reaction over the radioactive colloid (Fig. 2*C*) has almost the same density as the equivalent layer of the emulsion in the ordinary preparations (Fig. 2*A*) for the same exposure.

Besides spontaneous fog, some fogging may be produced by various physical agents, such as cosmic radiation, pressure, and elevated temperatures. Similarly, chemical agents may be a cause of fog,[98] e.g. fumes (hydrogen sulfide) and especially hydrogen peroxide, which is slowly produced by many types of containers (wood, paper, etc.). Artefact images may also be due to the chemical action of the tissue sections on the emulsion.[17] All types of chemical fogging are easily prevented by keeping the preparations in the cold throughout exposure (1–4°C.). As an added precaution against the action of the tissues on the emulsion a thin layer of celloidin is interposed between section and emulsion. This layer has a negligible thickness, as shown by profile sections of radioautographs (Fig. 2).

From these considerations it may be concluded that the emulsions giving the best localization will contain a high concentration of small uniform grains, with low background fog, and will have been sensitized to the photographic action of β-particles. These emulsions must be handled and processed so as to obtain the maximum contrast and to prevent an increase in the background fog. The practical application of these requirements will be discussed in the following section on methods.

METHODS OF RADIOAUTOGRAPHY

To insure that the localization of the radioelements is not modified by the handling of the tissue, careful controls are required. In fact, the retention of each radioactive element or compound repre-

sents an individual problem to which the basic methods must be adapted. For example, in the radioautography of radiophosphorus in bones, the tissues may not be stained with hematoxylin prior to exposure because the acid present in the staining solution leaches out the phosphate. Similarly, sections must be prepared by the freezing technique and not by paraffin embedding, when it is desired to localize fat soluble substances. To locate most water soluble substances, the tissues must be fixed by drying in vacuo at low temperatures, and so on.

The resolution of the radioautographic images varies according to the method used. The "*contact radioautograph*" technique, in which the section is placed close to a photographic film or plate (Fig. 11), requires no special equipment and can be routinely used in any clinical laboratory, but gives a rather poor resolution because of the significant interspace between emulsion and specimen.

The interspace has been practically eliminated in newer techniques, in which section and emulsion are bound together permanently. The tissue and the radioautographic image can then be viewed together under the microscope. This was first carried out by coating histological sections with fluid photographic emulsion,[7] a technique which was later improved by staining the sections before coating with the emulsion ("*coated radioautograph*"[57]). Another form of this technique was to coat the sections with a stripping emulsion instead of fluid emulsion.[10A,13A,15,62,75] Finally, a similar result may be attained by floating paraffin sections of tissues over a photographic plate and staining after development and fixation ("*mounted radioautograph*"[32,34,78]). By these techniques images less than 10 micra apart can be resolved with the possibility of intracellular localization in favorable cases (Fig. 75).

All these methods have been carried out in this laboratory and have been found to give reproducible results. A comparison of the results of each method on the same thyroid is shown in Plate 1. As a preliminary to their detailed description, relevant information on the preparation of the specimens may be of use.

A. *Preparation of Tissues.*

In the case of soft tissues, paraffin or celloidin sections are prepared in the routine histological manner and dehydrated with or without staining. The thinner the section, the better the resolution. For practical purposes, 5 μ paraffin sections and 10 μ celloidin sections seem to be most convenient.

In young animals, it is possible to cut bones and even teeth after celloidin embedding according to Bloom's method[60]. However, the tissues such as mature tooth or bone must be ground to a smooth surface on a fine revolving stone. Examples of such grinding machines may be found in the literature.[50,54,89] In this laboratory, the sample is glued with Duco cement on a microtome mount, which is then clamped on a microtome facing a motor-driven emery stone. After polishing one side with a fine stone cooled by a stream of water, the sample is removed from the mount, glued to a microscope slide, polished on the other side, and then placed in contact with a photographic plate for exposure.

Large specimens of soft tissues may be frozen, ground in the same way or sectioned with a chilled blade or fine electric saw while being kept in the frozen state, and thus applied to the photographic emulsion. This technique has been used in the localization of radioelements in amputated limbs, whole mice, etc.[50]

B. *Radioautographic Procedures* (Plate 1).

1. The contact method (Fig. 11–13). In this method a microscope slide, bearing a radioactive tissue section, is placed against a photographic film or plate and the two are kept in close contact by pressure. This method is most commonly used for the radioautography of hard structures or frozen tissues prepared by grinding or cutting.

The steps of the "contact" method used here are as follows:

(1) The sections are coated with celloidin by being dipped twice in a 1 per cent ether-alcohol solution following staining and passage through 95 per cent and absolute alcohol. The sections are then dried overnight to insure hardening of the celloidin.

(2) The surface of the section to be radioautographed is examined under a dissecting microscope for dust granules and particles that may make for uneven contact.

(3) In the dark room, using a suitable safelight, the section on the slide is placed next to a photographic plate or film (E.K. contrast lantern slide, X-ray film, etc.). A very close contact is obtained by applying equal pressure to both sides of the plate and slide with the help of light-tight roentgen-ray pressure cassettes. A sheet of cellophane may be interposed between specimen and film. The cassette is stored at 1–2°C. for the duration of the exposure.

(4) After exposure, the photographic plate

PLATE 1

This plate illustrates the various types of commonly used radioautographic methods. The schematic drawings on the left indicate the relationship of radioactive tissue section and photographic emulsion. The photographs on the right represent preparations made by the various methods from the same rat thyroid. The animal was sacrificed twenty hours after injection of 20 μc. of carrier free radioiodine.

FIG. 11. Schematic drawing indicating the relationship of the radioactive tissue section to emulsion in the *contact method*. The section is placed in close contact with, but not attached to the emulsion. The two groups of black granules indicate the response of the emulsion to two radioactive areas in the tissue.

FIG. 12. Section of thyroid from the experimental animal. Hematoxylin and eosin stain. ×25.

FIG. 13. Contact radioautograph obtained by placing the above section (Fig. 11) in contact with an E.K. contrast lantern slide plate. ×25. A comparison with the section shows spot-like reactions, each one of which is due to a thyroid follicle. The parathyroid (middle left) does not react. This picture represents the maximal useful magnification for a contact radioautograph. To obtain a resolution sufficient to distinguish the individual reactions of follicles as small as those of the rat, the preparations must be in closer contact with the emulsion.

FIG. 14. Two schematic drawings illustrating the *mounting method*. The upper diagram represents the section mounted on the emulsion, after development of the radioautographic granules. The lower diagram represents the final preparation after the section has been stained and protected with a coverslip. It is apparent that an intimate union between emulsion and section is obtained. Note that the developer must penetrate the section to reach the emulsion.

FIG. 15. Mounted radioautograph (E.K. medium lantern slide) of thyroid from the experimental animal. Hematoxylin stain. ×25. The occasional round light areas are due to lack of development of the emulsion under certain follicles due to the failure of penetration of the developing solution. The grayish background is due to the staining of the emulsion gelatin.

FIG. 16. High power of a portion from Figure 15. ×425. The concentration of silver granules over the colloid of the follicle is clearly visible. This concentration should be compared to that of the background fog, as seen over the unreactive tissue in the upper left hand corner.

FIG. 17. Schematic drawing of a preparation made by the *coating method*. The stained radioactive tissue section is coated with a layer of liquid emulsion. A thin protective coat of celloidin between the section and the emulsion preserves the stain from effects of developer and fixer.

FIG. 18. Coated radioautograph (E.K. medium lantern slide emulsion diluted 1 in 8 with 1 per cent duponol) of thyroid from the experimental animal. Hematoxylin and eosin stain ×25. There are no processing artefacts. The histological detail of the section is visible through the unstained emulsion.

FIG. 19. High power of a portion from Figure 18. ×425. The reaction is localized in the colloid, with little fog being apparent over the unreactive tissue in the upper left corner.

FIG. 20. Schematic drawing of a preparation made by the *strip film method*. The principle is the same as that of the coated radioautograph with stripping film being used instead of melted emulsion.

FIG. 21. Strip film radioautograph (Ilford halftone stripping film) of thyroid from the experimental animal. Hematoxylin and eosin stain. ×25. The appearance at this magnification is very similar to that of the coated radioautograph.

FIG. 22. High power of a portion from Figure 21. It can be seen here that the granules of this type of emulsion are much smaller than those of the medium lantern slide emulsion (Fig. 19).

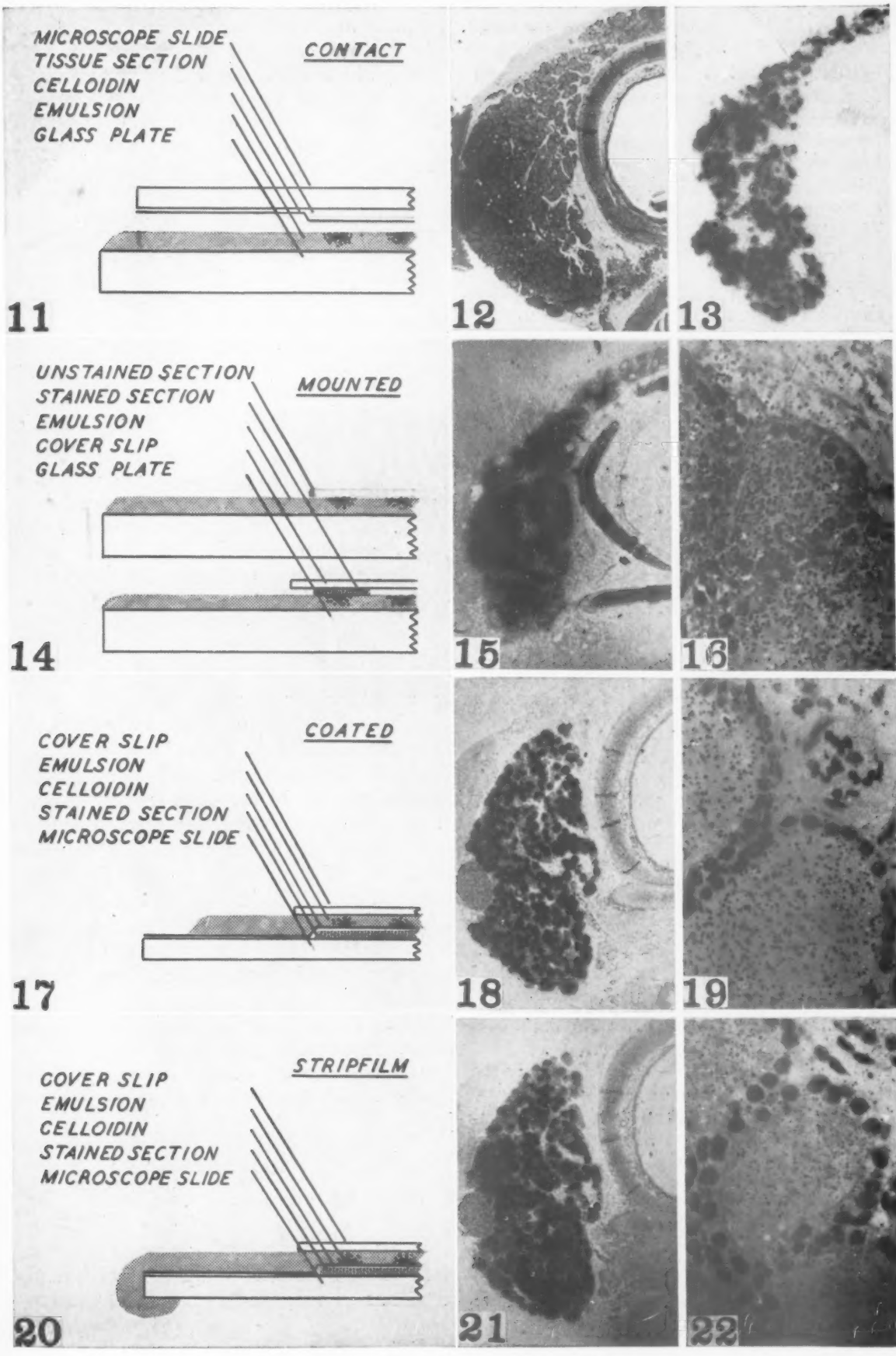


PLATE I. (See facing page for legends.)

or film is developed and fixed according to routine photographic procedures.

The resulting radioautograph (Fig. 13) may be superimposed on the section (Fig. 12) and both are examined simultaneously under the microscope. It was found useful to cover the radioautograph with a histological coverslip after deposition of a drop of Canada balsam on the dry emulsion.

This technique has the advantage of simplicity, but the resolution is low and the comparison between specimen and image under the microscope is difficult, except at low magnifications. Techniques have been suggested to facilitate the comparison,[14] but they are rather cumbersome.

2. THE MOUNTING METHOD (Fig. 14–16). This method, in which the section is mounted directly on a photographic plate, has been used quite extensively in the radioautography of clinical thyroid material. This method has also been successfully used for the localization of radioactivity in smears of blood, bone marrow, etc. In this case the material is smeared directly on the surface of the emulsion in the darkroom. The staining of the mounted sections is carried out after exposure and development. The following are the details of the technique as adapted for use in this laboratory:

(1) Unstained strips of tissue sections are floated in a 40°C. water bath to remove wrinkles from the tissue. They are then transferred to a bath of distilled water at 18–20°C., and all subsequent work is carried out in the darkroom at more than 3 feet from a Wratten No. 1 safelight. From the water bath the sections are floated onto photographic plates (medium contrast and contrast lantern plates, NTB film, etc.). When the excess water drains off, the section adheres to the emulsion.

In the case of smears, the blood or other material to be studied is spread evenly on the surface of the selected emulsion. The smear is rapidly dried in the air.

(2) The plates are stored at 1–2°C. in light-tight jars containing a drying agent for the duration of exposure.

(3) The sections are deparaffinated prior to development by being placed for one minute in each of two changes of absolute xylol. The xylol is allowed to evaporate completely in a well ventilated darkroom. Fifteen minutes is usually sufficient. In the case of smears this step is omitted.

(4) The plates are developed and fixed according to routine photographic procedures, all solutions being kept at 18–20°C.

(5) After being washed in running water, below 20°C. for 30 minutes, the plates are placed in dilute solutions of hematoxylin stain in the cold room (1–2°C.) and left overnight. The use of dilute solutions prevents a heavy staining of the emulsion, obscuring the radioautograph. Recently a mixture of metanil yellow and iron hematoxylin has been recommended as being less absorbed by the emulsion than routine hematoxylin.[38] For staining prior to development, hot carbol fuchsin-neutral red has been found to give stained sections which resist the destaining action of the developing reagents.[28]

(6) The plates are then dehydrated in 95 per cent alcohol, absolute alcohol, alcohol-xylol, and three changes of xylol. After immersion in a dilute solution of balsam for at least 5 minutes, the section is mounted in balsam under a coverslip.

The advantage of this method is its relative simplicity. There are, however, several disadvantages, such as: (1) the failure of the developer to penetrate the tissue uniformly, leaving some exposed areas underdeveloped (Fig. 15); (b) the tendency of the gelatin to stain with the tissue dyes obscuring the radioautograph to some extent (Fig. 15); and (c) the occurrence of emulsion blackening due to the chemical action of the tissue. These possibilities are eliminated in the "coating methods." It must be emphasized, however, that the preparations obtained by this technique are often more satisfactory under high than under low magnifications (Fig. 16).

3. THE COATING METHOD (Fig. 17–19).

(a) *Fluid emulsion:* In this method, the section is covered with either a fluid emulsion or a stripping emulsion removed from its backing. The method as used with fluid emulsion is very satisfactory for research

purposes, because of the possibility of controlling the thickness of the emulsion.

The thickness of the emulsion (estimated as indicated in the legend of Fig. 2) was found to be equal to 18–22 μ for two drops of undiluted medium lantern slide emulsion and 27–34 μ for three drops of this emulsion.[13B] Thinner emulsion coats are obtained by diluting the emulsion as explained below.

(1) The sections, stained or unstained, are coated with celloidin as in the contact method. The sections may be further protected by dipping the slides in a 1 per cent solution of Goodrich Geon Resin 200×20 in 90 per cent xylol-10 per cent methyl-ethyl ketone, four hours after the first coat of celloidin.[13B]

(2) The area of the slide to be coated (usually about 1 square inch) is defined with a diamond pencil. The material is then taken to the darkroom where work is carried out at a distance of at least 3 feet from a Wratten No. 1 safelight.

(3) Bulk emulsion (e.g. Ansco radioautographic emulsion A) or emulsion removed from photographic plates (E.K. medium lantern slide or other) is scooped into a 50 cc. beaker. In removing emulsion from lantern slides, the plates are soaked in distilled water for 10 minutes at 19±1°C. The emulsion is then sufficiently hydrated and softened and may be scraped into the beaker with a plastic knife or with any straight-edged piece of glass. One 3 by 4 inch lantern slide plate yields sufficient emulsion to coat 3 or 4 slides.

(4) The beaker is then placed for 15 minutes in a water bath kept at 37°C., during which time the emulsion becomes sufficiently fluid for application. Some improvement of the resolution (see theoretical section) may be obtained by thinning the emulsion. Thus, the lantern slide emulsion has been thinned with good results by adding 6 cc. of distilled water and 1 cc. of a 1 per cent solution of the wetting agent (duponol C) to 1 cc. of melted emulsion (Fig. 18–19).

(5) While the emulsion is being melted, the stained slides are warmed on a leveling table which consists of a glass top with a heating element under one end, adjusted to give a temperature of 37°C. at the surface of the glass. The whole is set on leveling screws and made horizontal with the aid of a spirit level.

(6) The warm slide is taken in one hand. Two drops of emulsion for every square inch of slide to be covered are applied with a medicine dropper held in the other hand. All the air must be expelled from the dropper to prevent the occurrence of bubbles in the emulsion.

(7) The drops are spread evenly and quickly with a camel's hair brush. The dropper and camel brush are returned to containers which are also kept at 37°C.

(8) The slide is then rotated from side to side along its long axis so that the emulsion flows from edge to edge, making an even film.

(9) The slide is returned to the warm side of the leveling table for 30 to 60 seconds to insure uniformity of emulsion and is then slid gently to the cool side of the plate. After 30 minutes the emulsion has hardened sufficiently so that the slides may be stored in light-tight slide boxes.

(10) The slides are always stored in a horizontal position to prevent any displacement of emulsion. The boxes are then placed in light-tight jars which contain a drying agent (calcium chloride). The jars are large candy jars, painted inside and out with black paint. They are placed in the cold (1–2°C.) for the duration of exposure. If the slide boxes are made of waterproof material (e.g. plastic) the drying agent may be placed directly in them. The boxes may then be bound with waterproof tape and stored in the cold.

(11) Development is in Kodak D-72 at 18–20°C. for 1½ minutes, with fixation in acid fixer for 3–6 minutes. Fixation must be short to prevent or reduce the removal of the stain from the sections.

The slides are washed for 15 minutes in water below 20°C. to prevent buckling and peeling of the emulsion. They are then dehydrated in 95 per cent alcohol, absolute alcohol, alcohol-xylol, and three changes of xylol. Three minutes in each bath is necessary for complete dehydration. To prevent artefacts the slides are immersed in a 1 per cent solution of balsam diluted with xylol for at least one hour, and sometimes overnight. Long periods of time are recommended for hard tissues. Slides should at all times be kept horizontal.

(12) The sections are mounted in balsam under a coverslip and the preparations allowed to dry at room temperature.

It should be emphasized that scrupulously clean glassware and brushes should be used, as both dust and remnants of old emulsion will result in artefacts and poor preparations.

(b) *Stripping film emulsion:* Instead of using fluid emulsion, the sections may be coated with a *stripping film*, such as Ilford special half tone stripping film or Kodak NTB stripping film. The Ilford film, which is routinely used in this laboratory, consists of a photographic emulsion mounted on a thin gelatin base which is in turn mounted on a glass support. The film and gelatin base are easily stripped from the glass and may be applied to the radioactive tissue section (Fig. 20–22).

This film is removed from its glass support by cutting the emulsion along the three edges of the glass plate. The emulsion is then slowly peeled off to about 1 inch from the edge and, with the side that formerly adhered to the glass facing upwards, kept for 5 minutes in a shallow dish containing a 1 per cent solution of duponol C at 18–20°C. The microscope slide bearing the section is slipped underneath the emulsion and lifted together with the emulsion out of the water. The emulsion is trimmed to a size slightly larger than that of the slide, so that the edges may be folded underneath to insure adherence. Another way to make the emulsion adhere to the slide is to use glass slides that have been dipped in gelatin prior to mounting the sections on them.[10A] The slides are then stored dry at 1–2°C. as above. In this method, the gelatin base is on the side of the emulsion opposite the section.

This strip film technique results in a preparation in which the section and emulsion are in intimate contact. When the NTB Kodak stripping film is used, its plastic base cannot be placed upwards as it is not permeable to the developer. The base must be placed between the section and emulsion, a procedure which results in a poorer resolution due to the increased interspace. New NTB stripping films with a permeable base (NTB_2) are now available.

The difficulty of the coating technique and its variants lies in the fact that the sections must be stained before being coated. Therefore, the preparations in which the radioactivity material may be displaced by the staining procedure must be autographed in the unstained condition. However, in many cases, a non-interfering staining method has been found,[77,78] for example, safranin, or basic fuchsin, may be used instead of hematoxylin in the case of undecalcified bones.[60]

4. THE INVERTING METHOD. Another way of obviating this difficulty is to invert the preparation formed by the section and the emulsion[8,62]. The method[8] giving the best resolution requires the use of a special emulsion, Kodak matrix. An unstained tissue section, previously covered with celloidin, is coated with matrix emulsion. After exposure and development the preparation is placed under water and the emulsion is lifted from the slide using a razor blade, with the tissue section adhering to its undersurface. The complex is then inverted and fixed on a clean slide, section side up. The free edges are sealed with 1 per cent celloidin, which is allowed to dry completely. The section may now be stained with ease, since the celloidin protects the emulsion from the action of the dyes (see Fig. 37). The preparation is mounted under a cover slip using Canada balsam.

C. *Technical Considerations Common to all Methods.*

1. THE SELECTION OF THE EMULSION. The selection of the emulsion is based on the requirements outlined in the theoretical section.[7*] Three varieties of emulsions may be considered:

(a) *Roentgen-ray type:* This is a fast emulsion, consisting of coarse grains, which gives a poor resolution, but is used for preparations containing a low intensity of radioactivity. This may be estimated by centering the sections on the sample holder trays currently used with Geiger counters, no special equipment being required. Low counts do not necessarily indicate the need for a roentgen-ray emulsion. Thus, a section which gives a background count by the Geiger counter may show areas of focal

[7*] Details of the various characteristics of β-sensitive emulsions may be found in Table 25 and Figure 43 of Yagoda[98] and in a leaflet, "Sensitized Materials for the Scientific and Industrial Laboratory" put out by Eastman Kodak Company.

concentration of radioelement even with a relatively insensitive fine grain emulsion.[38]

Roentgen-ray emulsions are available either as films, of which there are many varieties (Ansco, E.K., Ilford) adaptable to the contact and mounting methods, or in bulk (Ansco radioautographic emulsion A) for the coating method.

(b) *Lantern slide type:* This emulsion, which is finer grained and about 10 times less sensitive[64] than the roentgen-ray emulsions, has been widely used for all types of methods, with excellent results. It is available as contrast or medium contrast lantern slides (E.K., Ilford, etc.) for the contact or mounting methods. For the coating method, the emulsion may be scraped from plates such as the E.K. medium contrast lantern slides (E.K. contrast lantern slides are not suitable). The Ansco radioautographic "B" and "C" emulsions, available in bulk, are somewhat comparable.

(c) *Special fine grain emulsions* (nuclear emulsions): The first emulsion of this type which was available was that of Ilford half tone stripping film. This is rather less sensitive, has finer grains than the lantern slide emulsions (as may be seen by a comparison of Fig. 19 and 22), and theoretically should give a better resolution. There are now a series of nuclear emulsions, the E.K. NTB 1, 2 and 3 as well as a stripping plate material prepared by the British branch of the E.K. Company. All may be used for the mounting, coating, and stripping method. Some difficulty has been experienced in melting the NTB emulsion, but this difficulty will probably be corrected in the future, thus making this material suitable for the coating technique. The sensitivity of the NTB plates increases with their number (1, 2 and 3), but the fog also increases. Sharpest images have been obtained with NTB_2.[8*]

In using any emulsion, fog may be kept to a minimum by using the following controls. First, the plates, films, or bulk emulsion must be sampled for low background fog, as the fog level was found to vary widely in several samples of the same material. Second, care must be taken to avoid heat above 37°C. throughout the radioautographic procedures involving melting of the emulsion. Similarly, during exposure, the preparations should be kept in the cold (1–4°C.), a cold room or refrigerator being satisfactory. A deep freeze (−10°C.) has been used here and appears satisfactory, but many emulsions are said by the manufacturers to be adversely affected by such low temperatures. Third, a rather short development is to be preferred, its duration being predicted on the basis of emulsion thickness. It is, however, important in the coating and stripping methods to make sure that the developer has penetrated the whole thickness of the emulsion. This point can be checked under the microscope by ascertaining that the maximum number of grains is present close to the specimen. For active preparations, the use of diluted emulsion will reduce the density of the background fog.

2. The duration of exposure. It is important to keep the exposure to a minimum, as overexposure results in a more diffuse image with corresponding loss in resolution (Fig. 8). In addition, the histological details of the section tend to be obscured by the silver granules.

It is customary in routine work to obtain an approximate estimate of the activity of the sections under the Geiger counter. As a rough working rule, preparations containing a low activity will require long exposures, although it hardly seems useful to expose for more than 4 half-lives. It must, however, be noted that predictions of exposure time on the basis of activity per unit area[64] may result in overexposure at the sites of high activity and underexposure of the low radioactivity concentrations.

In practice, a series of radioautographic preparations of the same tissue are made

[8*] At the time of writing (1949) we had had experience only with the Kodak NTB 1 type of emulsion. The NTB 2 and NTB 3 nuclear emulsions have been examined since and found to have a higher sensitivity.

and developed at various time intervals after the beginning of the exposure, until an optimum radioautographic image is obtained. These "test slides" are usually unstained to facilitate the detection of small amounts of blackening. The experimental slide itself will usually be stained.

During exposure, it is essential to store the preparations in a dry container kept in a refrigerator or preferably in a deep freeze, especially for long exposures. In this manner, the production of fog or chemical artefacts, as well as the fading of the latent image, is minimized.

D. *Quantitative Radioautography.*

Some preliminary work on the quantitative estimation of the density of the radioautographic images has been carried out. Several methods are available:

1. The measurement of photographic densities using a photometer is satisfactory for work at *low magnification.*[3,27] The magnified image is projected onto a frosted glass, and estimated as "densities" (which are measured as the log of the intensity of incident over transmitted light).

The photographic density in a certain area is known to be practically directly proportional to the mass of silver deposited in the emulsion below that area.[51] As a result, assuming that there is a constant mass of silver per developed grain, the photometric density is proportional to the number of grains in a given depth of emulsion.

2. The counting of photographic grains in an area outlined by a micrometer placed in the ocular is a satisfactory method to estimate densities at *high magnification.* This procedure is being used by Pelc and Spear[76] and in this laboratory. The method used here consists in counting grains at various levels of the emulsion overlying a reactive zone. Thus, the number of grains per unit area was estimated at distinct emulsion levels over the center of colloids from thyroids of I^{131}-treated rats. The relative counts obtained for colloids of various diameters were found to be in good agreement with theoretical calculations of the mean radiation densities at distinct emulsion levels, as derived from formulations such as used in Figure 7, Table II for a cylindrical source of radioactivity.

The results obtained by these methods may be expressed in several ways. The simplest consists in comparing two structures of the preparation reacting with a different intensity, such as thyroid nodules and normal paranodular tissue, as done by Dobyns and Lennon,[26] who calculated the ratio of their densities. A more complex method consists of comparing the radioautographic reactions to standard reactions due to known amounts of radioelements autographed under the same conditions.[31]

It is obvious that true comparisons are only made in sections with identical geometric relations in regard to the specimen and emulsion thickness, the interspace between them, and the geometrical configuration of the source. In theory the stripping film method lends itself best to quantitative radioautography, since in the contact method, the interspace varies; in the mounting method, the degree of development varies due to interference of the section with the passage of the developer into emulsion, while in the case of fluid emulsion coating, the thickness of the emulsion varies somewhat. In practice, however, the coating technique is quite suitable for the counting of granules. The results, in which a good agreement was found between grain counts at various emulsion levels and theoretical calculations, were obtained in radioautographs coated with melted Ilford nuclear emulsion. Nuclear emulsions are the most satisfactory for grain counting, because of the regularity of the grains.

Another important consideration results from the data in the footnote 6*, showing that the density remains proportional to the intensity of the source, and thus to the concentration of the isotope, only when the exposure is kept to a minimum. Otherwise the relationship between density and concentration is more complex.

3. With the availability of emulsions

which show β-tracks, preliminary work has indicated that counting the tracks per unit area may be used as a method of quantitative radioautography.[18]

RADIOAUTOGRAPHIC RESULTS

When classifying radioautographic results, it is tempting to organize them according to the substances injected. However, since most injected materials are rapidly transformed into their metabolites, the classification was organized according to the nature (known or presumed) of the substance in the section *responsible for the radioautographic reaction.* Some knowledge of this sort is indispensable if a radioautograph is to have any physiological meaning. Broadly speaking, most of the results to date are referable to proteins or to inorganic salts.

It was found necessary to make a preliminary distinction between the substances that are normally present in the tissues and those which are foreign to the body, as in the case of pharmacological or toxicological studies. It so happened that practically all work done with foreign substances was done by the "contact method," while most work done with physiological substances took advantage of the finer methods of radioautography. The illustrations will bring out clearly the advantages of the latter.

A. *Foreign Substances.*

The first part of this section deals with heavy radioelements produced in the course of the development of atomic energy. The second part refers to organic substances synthesized from radioelements.

1. Inorganic. The elements used as such may be divided into two main groups: (a) the raw materials for atomic reactors, which fall into a group of the periodic table analogous to the rare earths, known as the "actinide series," and which include uranium, plutonium, americium and curium; (b) the fission products, which fall into several groups: (1) the "lanthanide series" of rare earths, of which the distributions of lanthanum, cerium and praseodymium have been investigated along with a related element, yttrium; (2) the elements related to calcium, that is, strontium, barium and also radium which, while not a fission product, may be included here for the sake of convenience.

The *actinide and lanthanide groups* of elements, administered as their ions, are found to be localized primarily in bone where they may remain for considerable periods of time.[47] From the radioautographs, it may be seen that they locate in the growing areas of the bone, namely the epiphyseal plate with a predominance on the subepiphyseal (or metaphyseal) spicules, the head of the epiphysis and under the periosteum and endosteum (Plate 2). Some differences between the ions may be made out; thus americium[81] and curium,[83] but not plutonium or uranium, tend to show accumulations about the small vessels of the bone cortex (Fig. 29 and 30). In the case of uranium[71] its deposition at the sites of mineralization causes radiation damage which results in an abnormal thickening of the shaft and persistence of metaphyseal spicules (Fig. 27 and 28). Thus, the members of the actinide series tend to retain their location in the endosteal and metaphyseal surfaces, and therefore may constitute a hazard to the bone marrow (Fig. 34). On the other hand, Copp *et al.*[22] showed on bone radioautographs that a demineralizing diet followed by remineralization causes the radioactive material to be buried within the depths of the bone.

The Berkeley group has also investigated radioautographically the deposition of these substances after inhalation. They found these radioelements in the lung alveoli and the epithelium of the air passages, from which they are rapidly removed by ciliary action.[82]

In a study of the histopathologic changes due to radiations from these substances, Bloom and his co-workers[12] have made considerable use of the radioautographic method. The pictures they found in the

bone (Fig. 35–36) are similar to those of the other workers who did not use highly radioactive doses.

The *elements related to calcium* used in radioautography have mostly been strontium and radium which, upon administration in ionic form, localized mostly in the growing ends of the bone. This has been indicated by the results of several publications on strontium[12,22,37,47,74] and radium.[12,20,65,92] The deposition of the strontium ion is impaired by a low phosphorus diet, as only the mineralized areas of the bone (such as the shaft which stains black with silver nitrate, Fig. 31) show the entry of radiostrontium (Fig. 32). The areas of recent formation, such as the metaphysis, do not stain with silver nitrate nor show a radioautographic reaction. In contrast, the low phosphorus diet did not prevent the fixation of the elements of the previous group in the metaphysis (Fig. 33, 34).[22] Recently, *gallium*[30A] has also been found to deposit in bones.

The distribution of *polonium* in the body has been covered in a previous

PLATE 2

FIG. 23. Longitudinal section of distal end of femur of a growing rat injected intraperitoneally with 1.5 μc. of Ur^{233}, and sacrificed four hours after injection.

FIG. 24. Contact radioautograph (E.K. x-ray plate) of Figure 23. The most intense radioautographic reaction occurs on the diaphyseal edge of the epiphyseal plate, with a lesser one of the subepiphyseal spicules. Some reaction is also noted in the diaphyseal bone, as well as the trabeculae of cancellous bone in the head of the epiphysis.

FIG. 25. Longitudinal section of the femur of a growing rat injected with 1.5 μc. of Ur^{233} and sacrificed five days after injection.

FIG. 26. Contact radioautograph (E.K. x-ray plate) of Figure 25. The radioautographic reactions are now slight on the diaphyseal edge of the epiphyseal plate and intense on the underlying spicules. The diaphyseal reaction seems mostly periosteal. A reaction is present in the cancellous bone of the epiphyses.

FIG. 27. Longitudinal section of the femur of a growing rat injected with 1.5 μc. of Ur^{233} and sacrificed forty days after injection.

FIG. 28. Contact radioautograph (E.K. x-ray plate) of Figure 27. The areas of bone fixing uranium soon after injection were not resorbed, thus the large spot visible in the marrow cavity on the middle right is due to unresorbed uranium-bearing spicules. At the proximal end of the shaft, bone has been deposited externally to the periosteal line of uranium deposition but has failed to resorb at the marrow surface, hence the thickening of the diaphyseal wall (Fig. 27). (Fig. 23–28 from Neuman and Neuman[71] 1948.)

FIG. 29. Shaft of bone of a rat injected intramuscularly with 10 μc. of carrier-free, $Cm^{242}Cl_3$, and sacrificed seven days after injection. Stained. ×38. The arrows point to small blood vessels.

FIG. 30. Contact radioautograph of Figure 29. The radioautographic reaction indicates the deposition of curium in the region of the small blood vessels. ×38. (Fig. 29–30 from Scott, Axelrod and Hamilton[83].)

FIG. 31. Femur of a rat weaned on a phosphorus-deficient diet at three weeks, injected with 5 μc. of Sr^{89} at five weeks and sacrificed one week later. Hematoxylin and eosin stain and silver nitrate. ×10.

FIG. 32. Contact radioautograph (no screen x-ray film) of Figure 31. The radioautographic reactions indicate the deposition of Sr^{89} in the bone salt remaining in the shaft, and practically none in the unmineralized osteoid matrix below the epiphysis.

FIG. 33. Femur of a rat weaned on phosphorus-deficient diet at three weeks, injected intramuscularly with 20 gms. plutonium at five weeks, and sacrificed one week later. Hematoxylin and eosin stain and silver nitrate. ×5.

FIG. 34. Contact radioautograph of Figure 33. The radioautographic reactions indicate heavy deposits of plutonium in the uncalcified osteoid matrix below the epiphysis and the endosteal region of the shaft. (Fig. 30–34 from Copp, Axelrod and Hamilton[22].)

FIG. 35. Femur of a young rat injected intravenously with 0.2 mg./g. of alizarin and 0.015 μc./g. of plutonium, and sacrificed twenty-four hours after injection. Undecalcified. ×8. The dark accumulations correspond to the areas of alizarin deposition.

FIG. 36. Contact radioautograph of Figure 35. The radioautographic reactions due to plutonium show a pattern of uptake similar to that of alizarin. The heaviest deposition is in the epiphyseal region just below the plate, with a less intense deposition on the subepiphyseal spicules and in the periosteal and endosteal regions. (Fig. 35–36 from Bloom—Histopathology of Irradiation.[12])

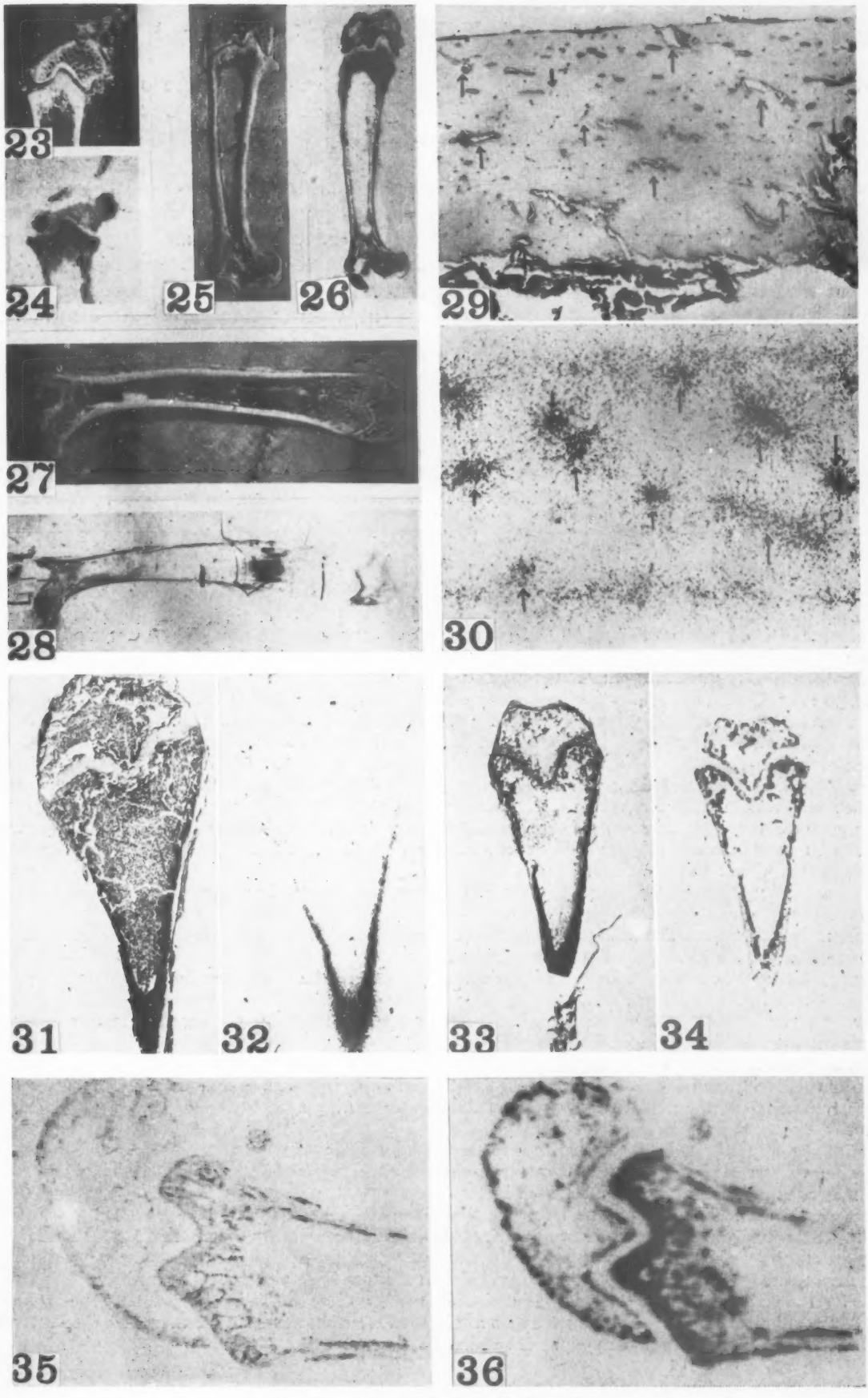


PLATE 2. (See facing page for legends.)

review,[42] but since that time Endicott and Yagoda[32] have published some fine pictures demonstrating the localization of this element in the glomeruli and distal convoluted tubules of the kidney.

The distribution of various radioactive inorganic material has been followed to determine their usefulness in therapy. These include colloidal preparations of chromic radiophosphate,[53] radiogold,[46] uranium oxide,[55] and gold thiosulfate[49] which have been shown radioautographically to locate in the cells of the reticuloendothelial system. As a result, some of these are being used in the treatment of malignancies occurring in this tissue. Similarly, Muller[67,68,70] has used macroradioautographs to investigate and control the use of radiozinc, in various forms, for the treatment of malignancy.

2. ORGANIC. Using mustard gas labeled with radiosulfur, and lewisite labeled with radioarsenic, Axelrod and Hamilton[3] obtained radioautographs of the radioactivity within the layers of the skin and the eye at various time intervals after local administration. Mustard gas was found to locate in the epidermis and the dermis of skin in humans and in the pig, with preferential localizations in hair follicles, sebaceous glands, blood vessel walls and fibrous tissue bands of the hypodermis (Fig. 65). Lewisite, on the other hand, was fixed

PLATE 3

FIG. 37. Inverted autograph (E.K. matrix emulsion) of endochondral ossification in the proximal tibial epiphysis from a 50 gm. rat given a subcutaneous injection of carrier-free radiophosphorus and sacrificed one hour later. Hematoxylin. ×100. The radiophosphate deposits in the area of hypertrophic cartilage, on the trabeculae separating the enlarged cartilage cells. Its presence is also noted in the endochondral bone spicules. (From Bélanger.[8])

FIG. 38 to 43. Coated radioautographs of various parts of the tibial diaphysis of 50 gm. rats at various time intervals after injection of 350 μc. carrier-free P^{32}. The periosteal and endosteal surfaces of the diaphysis have been outlined with india ink, the letter *P* marking the periosteum on the left and the letter *E* the endosteum on the right. The first row (Fig 38–40) illustrates the reaction of the funnel-like subepiphyseal region, the second row (Fig. 41–43), that of the cylindrical region of the shaft. Unstained. ×30. (From Leblond, Wilkinson, Bélanger and Robichon.[60])

FIG. 38. Funnel at five minutes after P^{32} injection. The reaction is located on the endosteal surface of the bone.

FIG. 39. Funnel at two days after P^{32} injection. The reaction is located in the bone substance at some distance from the endosteal surface.

FIG. 40. Funnel at eight days after P^{32} injection. The reaction is located in the bone substance and farther from the endosteum than in Figure 39.

FIG. 41. Cylinder at five minutes after P^{32} injection. The reaction is located on the periosteal surface of the bone. The spots in the bone substance correspond to blood channels.

FIG. 42. Cylinder at two days after P^{32} injection. The reaction is located in the bone substance at some distance from the periosteal surface.

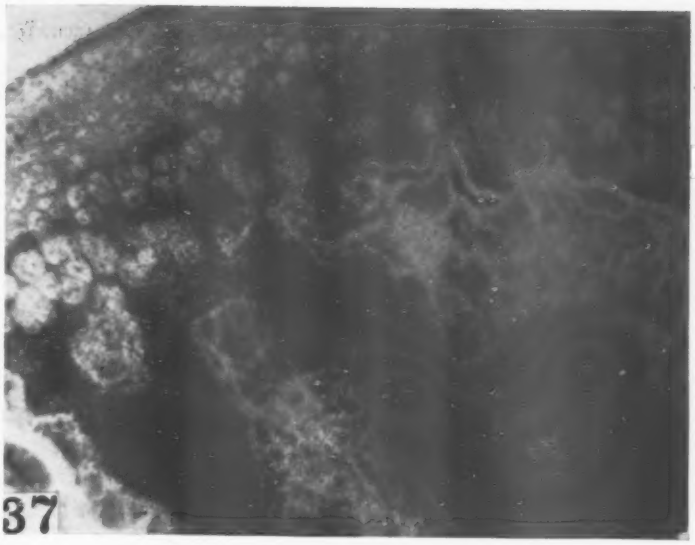
FIG. 43. Cylinder at eight days after P^{32} injection. The reaction is located in the bone and farther from the periosteum than in Figure 42.

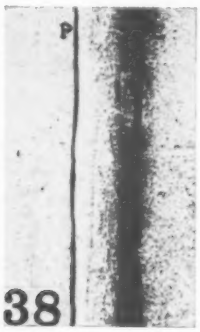
FIG. 44. Coated radioautograph of the cylindrical region of the shaft from the tibia of a 50 gm. rat subcutaneously injected with P^{32} and sacrificed two hours after injection. Safranin stain. ×100. At this early time interval, a diffuse reaction extends throughout the bone.

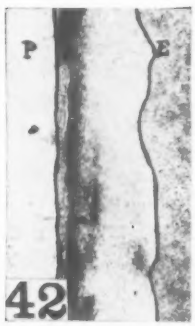
FIG. 45. Coated radioautograph of a longitudinal section of a tibia from a 50 gm. rat subcutaneously injected with 350 μc. carrier-free P^{32} and sacrificed four hours after injection. Safranin stain. ×8. The lower edge of the epiphyseal plate (hypertrophic cartilage) shows an intense dark line, beneath which a light reaction of spicules may be seen. This is followed below by a fairly intensely reacting area.

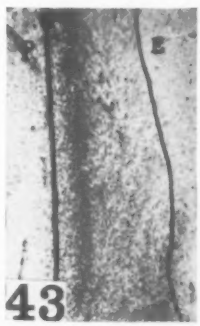
FIG. 46. Coated radioautograph of a longitudinal section of a humerus from a 50 gm. rat subcutaneously injected with 350 μc. carrier-free P^{32} and sacrificed two days after injection. Safranin stain. ×8. The lowest part of the spicules shows a reaction, which appears as a dark line extending across the spicules.

FIG. 47. Coated radioautograph of a longitudinal section of a tibia from a 50 gm. rat subcutaneously injected with 150 μc. carrier-free P^{32} and sacrificed eight days after injection. Safranin stain. ×8. The apparent downward motion of the dark line continues only on the spicules, which are close to the wall of the diaphysis, as the most central and most peripheral spicules have been resorbed.









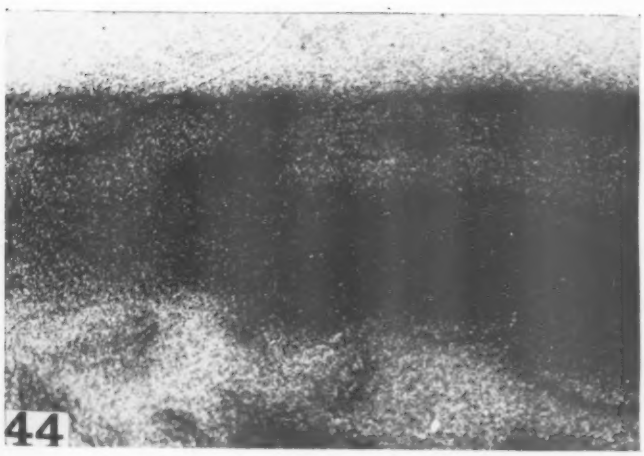


PLATE 3. (See facing page for legends.)

primarily in the epidermis and hair follicles. In the eye, these substances were traced to the surface of the lens.

With the help of a crude technique, the availability of the radioiodine of dithymol diiodide to the animal thyroid was demonstrated.[5]

It is evident from the few examples given that the radioautographic method presents a rather useful tool in the study of the toxic and pharmacologic behavior of materials foreign to the body, often providing information that could not be obtained by any other method.

B. *Physiological Substances.*

1. INORGANIC. *Phosphate ions* deposit as insoluble salts in bones and teeth. Since it is possible to preserve the insoluble salts in sections, radioautographic pictures of the areas of recent mineralization of bones and teeth may be obtained, as was indeed shown in the pioneer work previously reviewed.[42] Most of this work was done with contact radioautography and did not add much to the present knowledge of bone and tooth development. Neither did other recent studies which used this radioautographic method.

In order to obtain some insight into the dynamics of this phosphate deposition, serial radioautographic studies at various time intervals after the injection of the radioisotope were carried out by the coating and inverting methods. In the case of bone, a summary of the results obtained in the growing rat[60] are shown in Plate 3. Soon after injection, there are two kinds of reactions, diffuse and localized. The diffuse reactions extend throughout the bone, even in the shaft (Fig. 41 and 44), presumably as the result of an exchange between the labeled circulating phosphate and the surface phosphates of the crystals of bone salts. Within a short interval (less than a day) the diffuse reactions have diminished considerably, as may be seen in the shaft, by the comparison of Figures 41 and 44 with Figures 42 and 43. By that time, the localized reactions—which do not significantly decrease with time—stand out clearly. These reactions are due to the bone formed within a few hours following injection of P^{32} and presumably consist of insoluble crystalline salts labeled throughout. These are found in two locations: (1) *hypertrophic cartilage* of the areas of endochondral ossification, that is, the edges of the epiphyseal plate (Fig. 45) and the inner surface of the epiphyseal cavity (Fig. 37), and (2) the *new bone*, which is found in three locations, namely, at the surface of the metaphyseal spicules, under the endosteum lining the funnel-shaped subepiphyseal portions of the shaft, and under the periosteal surface of the more cylindrical portions of the diaphysis joining the two funnels. As growth proceeds (Fig. 46 and 47) the metaphyseal spicules containing the radioactive phosphorus are displaced downward by the formation of newer spicules, are resorbed along the central axis of the bone (Fig. 47) and come to form the upper part of the funnel portion of the shaft. The lower portion of the funnel continues to deposit bone on the endosteal surface with a resultant apparent movement of the layer of radioactive bone from the endosteal to the periosteal surface (Fig. 38–40). This apparent movement is also due to the resorption of bone from the periosteal surface since the distance between the radioactive bone lamina and the periosteum becomes smaller with time (see again Fig. 38–40). Conversely, in the cylinder (Fig. 45) the radioautographs (Fig. 41–43) show the apparent movement of the radioactive bone toward the endosteal surface, as a result of resorption in the endosteal region, and continued bone deposition under the periosteum. The net result of all these transformations is that the growth of a bone of this type may be represented by the gradual rise of an inverted truncated cone, attached at its narrow end to a cylinder. The cylinder, on the other hand, grows in diameter by the periosteal deposition of bone and in length by the transformations of the narrow ends of the funnels.[60]

Similar studies on the unerupted teeth

of the young hamster[9] have indicated that the radioautographic reactions in enamel and dentine are also due to both exchange processes (diffuse, labile reactions) and new formation of mineral crystals (localized, permanent reactions). The mineralization of dentine, as shown by the persistent reactions, occurs in the region immediately adjacent to the odontoblast layer, as a narrow band, while the phosphate deposition in enamel occurs at some distance from the ameloblast layer as a fairly broad band.

That the mineralization of the enamel occurs over a fairly broad area, while that of the dentine occurs only on its inner surface is also shown on radioautographs of unerupted teeth of monkeys[89] (Fig. 52 and 53).

In older animals, as shown in the jaw of the rat (Fig. 48 and 49), the erupted molar teeth show a reaction only along the inner surface of the dentine, thus indicating dentine formation. The incisor tooth, however, shows the formation of both dentine and enamel (Fig. 48 and 49).

The entry of labeled phosphate has also been followed radioautographically in urinary tract calculi.[24] The sharp localization of the reactions indicates that the stones are made up of discrete laminae whose phosphate is not exchangeable with that of adjacent layers. The entry of phosphate into the chambers of the eye and its behavior on the surface of the lens has been followed by Palm.[72,73]

The distribution of *radiocalcium* in bone is shown in only one published photograph[31] (Fig. 54), from which it may be seen that, in the rib, calcium is deposited primarily under the periosteum. *Radioactive carbonate* soon after injection may be found in the metaphyseal bone spicules and periosteal regions in newborn animals (Fig. 55). In older animals the deposition of radioactive carbonate has been mostly examined at late time intervals when, due to continued growth of the bone, the radioactivity is found mainly in the fully calcified shaft (see Fig. 5.99 in Bloom;[12] see also ref. 2, 11, 13). As a broad conclusion, these radioautographic data on bone would seem to indicate that the deposition of calcium, phosphorus and carbonate probably occur together and in the same manner, to unite in the formation of the complex mineral crystals of bone.

The diffusion of various radioactive ions has been followed in a few locations. Thus, *radioiodide* has been found to diffuse throughout the dentine and perhaps also the enamel of erupted teeth (Fig. 50 and 51).[6] *Radiosodium* behaves in a similar fashion in the teeth (Fig. 59).[10] These results indicate the extension of the extracellular spaces in the tooth, and show that the circulating ions can come in contact with the sites of mineralization where they are likely to be precipitated.

Radiosodium enters the eye (Fig. 56–58) in which it appears to reach the vitreous humor from the ciliary body and also from blood vessels in the vicinity of the optic nerve; entry into the anterior chamber seems to occur from the vessels of both ciliary body and the iris.[95] The only available data on the distribution of *radiopotassium* is its more or less even distribution through the brain tissue of the rat.[21] After the injection of *radiozinc*, as the sulfide, a diffuse distribution was found in the radioautographs of liver, spleen, and kidney.[69] *Radiocopper*, given carrier-free, was found to have a definite localization in the chick embryo, which showed a changing pattern as growth proceeded.[88] The authors point out the parallel between the copper distribution and that of cytochrome oxidase in the growing embryo.

2. Organic. Labeled organic compounds may be present in tissues, either because they were injected as such or because of the transformation of other labeled ions or compounds. The characterization of the compound(s) responsible for a given radioautographic reaction is often difficult. Failing this, the inclusion of the reactor as a member of a broad chemical group is indicated. The complete lack of knowledge

of the cause of reaction deprives it of histochemical significance, although some crude information may at times be deduced from the mode of preparation of the radioautographs.

Unidentified compounds: Pelc and Spear[76] were able to show that the radioautographic response was greater in cytoplasm than in nucleus in a cell cultured for forty-eight hours in a medium containing P^{32} (Fig. 60 and 61). Since treatment of the cells during preparation for radioautography probably removed most of the phosphate ions from the cells, it is likely that the radioisotope had been incorporated into organic molecules.

Similarly, after the injection of radiophosphate into rats, tissues which were

PLATE 4

FIG. 48. Ground section of a lower jaw of a 70 gm. rat injected with 0.5 mc. radiophosphorus containing 1 mg. carrier phosphate and sacrificed two hours after the injection. The jaw was dried without fixation. ×8. The section shows the incisor tooth cut along its length showing solid dentine on the right hand side and the roots surrounding the pulp on the left. A thin line at the lower edge of the dentine represents the enamel. Three erupted molars are visible on the upper left.

FIG. 49. Contact radioautograph (E.K. contrast plate) of Figure 48. The dentine of the incisor tooth and molars reacts only in the portion adjacent to the pulp. In the enamel organ only the newly formed enamel shows a reaction visible as the 1½ inch-long band on the lower edge of the picture. Some reaction is also visible at the surface of the bone spicules of the mandible.

FIG. 50. Ground section of the canine of an adult cat intraperitoneally injected with radioactive iodine (0.5 mc./kg. of body weight) and sacrificed twelve hours after injection. Unstained. *E*, enamel; *C*, cementum; *D*, dentine; *P*, pulp.

FIG. 51. Contact radioautograph (Ansco no-screen x-ray film) of Figure 50. Radioactivity is present in dentine and cementum and perhaps also in the enamel. The pulp area shows no reaction due to loss of the pulp in grinding. In the dentine there is an even density. (Fig. 50–51 from Bartelstone, Mandel, Oshry and Seidlin.[6])

FIG. 52. Contact radioautograph (E.K. M-plate) of a longitudinal section of an unerupted third monkey molar, nine days after intravenous injection of 15 mc. of radiophosphate. ×6. There is a diffuse reaction throughout the enamel (above) and a well localized reaction in the newly formed dentine (below).

FIG. 53. Contact radioautograph of (E.K. M-plate) of a longitudinal section of a developing third maxillary molar from the same animal as in Figure 52. ×6. The dentine has been removed, leaving only the enamel, which is particularly reactive throughout. (Fig. 52–53 from Sognnaes, Shaw, Solomon and Harvold.[89])

FIG. 54. Contact radioautograph (E.K. no-screen x-ray) of a resected rib of a dog given radiocalcium orally, and sacrificed twenty-one days after administration. The circles of graded blackening are calibration exposures increasing in magnitude by factors of 2, produced from plaster of paris blocks containing known amounts of Ca^{45}. (Dudley and Dobyns.[31])

FIG. 55. Coated radioautograph (E.K. medium lantern slide plate emulsion) of a section of bone from a newborn rat injected with carrier-free radiocarbon (as sodium carbonate) and sacrificed twenty-four hours after injection. Unstained. Most intense reactions are found in the bone spicules located below the epiphysis and periosteum (lower left) as well as in the epidermis. The two dark spots, labeled *EC* are pieces of epidermis cut parallel to the surface. Cartilage shows a moderate reaction, muscle a less intense one an connective tissue a slight one.

FIG. 56, 57 and 58. Contact radioautographs (dental x-ray film) of slices of frozen rabbit eyes, from animals sacrificed at various time intervals after intraperitoneal injection of 0.6 to 0.8 mc. of radiosodium per kg. of body weight.

FIG. 56—thirty minutes after injection. The radioactivity is predominantly in the ciliary body, choroid and optic nerve.

FIG. 57—one hour after injection. The radioactivity increases in the same three sites indicated in the previous figure, with some diffusion of the radioisotope into the vitreous. Diffusion in the anterior chamber seems to occur from the capillaries in the ciliary body.

FIG. 58—forty-eight hours after injection. The radioactivity is uniformly distributed throughout the eye, with exception of the substance of the lens. (Fig. 56, 57 and 58 from Sallman, Evans and Dillon.[95])

FIG. 59. Contact radioautograph (E.K. spectroscopic plates) of the ground section of the molar tooth of a dog injected with 20 mc. of radiosodium and sacrificed four hours after injection. The radioautographic image shows the presence of sodium in the tissue of the tooth (from Berggren[10]).

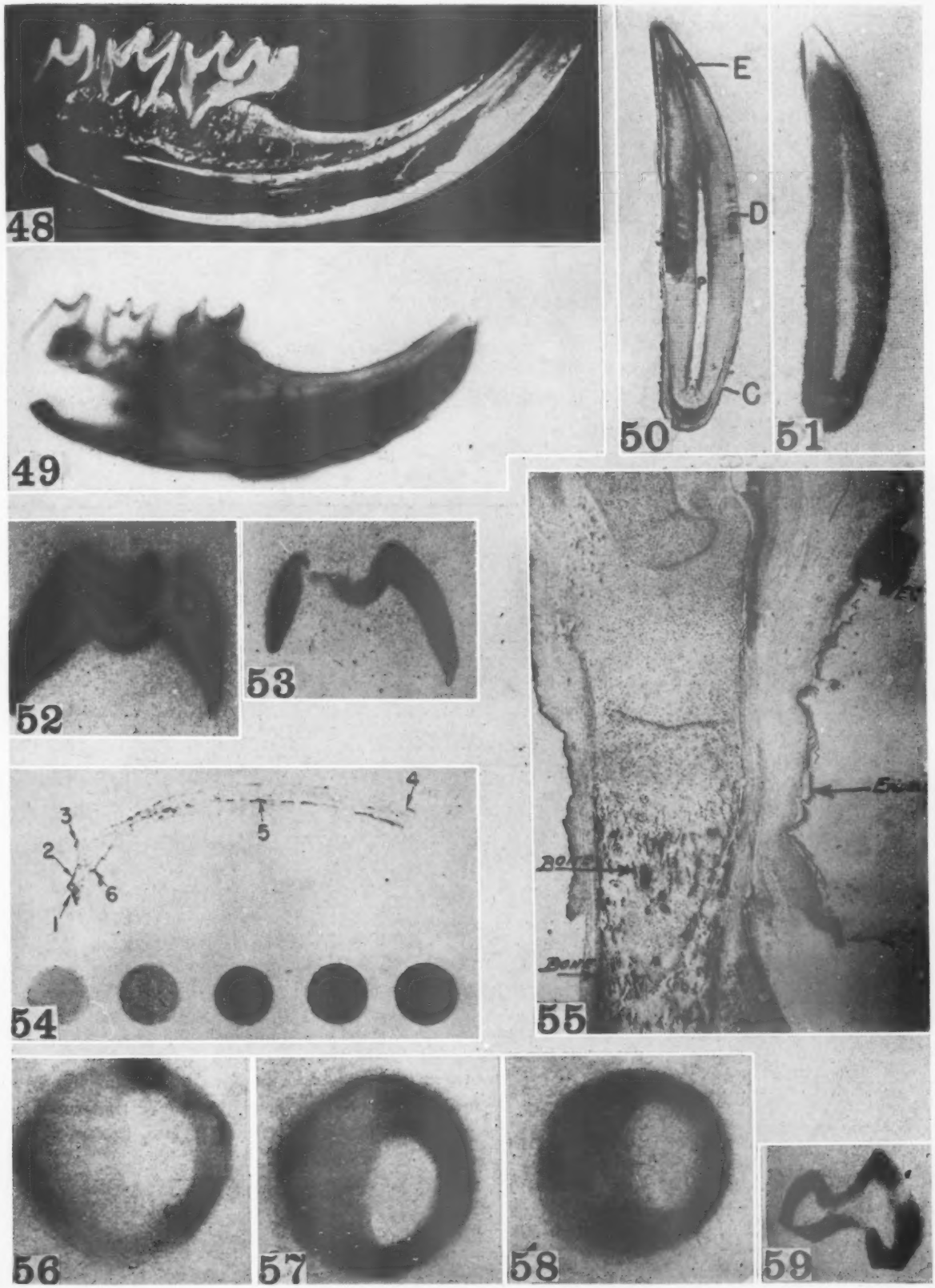


Plate 4. (See facing page for legends.)

fixed in Orth, sectioned in paraffin, and treated on the slide with ribonuclease, still gave a radioautographic reaction.[91] It was reasoned that in the course of histological processing, both phosphate ions and phospholipids were removed, while ribonucleic acid was hydrolyzed by ribonuclease and presumably lost. Of the remaining compounds, the amount of desoxyribonucleic acid and phosphoproteins was too low to produce the fairly intense reactions recorded. It was concluded that Orth fixation had made possible the retention of some acid soluble phosphorus, which was then responsible for the radioautographs (Fig. 62 and 63). An example of such preparations showed the presence of radioactivity in both the epithelium and muscle of the tongue (Fig. 62 and 63), as well as in intestine, kidney, liver, bone marrow cells, etc.

Finally, unidentified compounds of radiocarbon retained through histological processing—possibly proteins—were found in the epidermis (Fig. 55), in the kidney, and in many other organs of the newborn rat.

Carbohydrates and fats: The identified compounds include *carbohydrates*, such as radioactive glycogen which was demonstrated after the incubation of liver slices in a medium containing radioactive carbon as carbonate.[62] The radioautographs (Fig. 66) show that the radioactivity is located at the periphery of the lobule, and corresponds to the location of glycogen as demonstrated by specific staining.

The entry of phosphate into *phospholipids* has been claimed after the incubation of formalin-fixed slices of adrenal glands in a radiophosphate containing medium,[19] but the radioautographs are somewhat unconvincing.

A *steroid* closely related to estradiol, iodo-estradiol, was recognized by the radioautographic method in the connective tissue of the derma, with some reaction in mammary gland, intestine, and liver.[1]

Proteins: Of labeled biological compounds that may be present in tissues, radioactive proteins have been the easiest to follow since most proteins are precipitated in situ during fixation and retained in the tissue sections during histological and radioautographic procedures.

PLATE 5

FIG. 60. Chick fibroblast cultivated in a drop of fowl plasma to which was added one drop of radiophosphorus solution (100 μc. carrier-free radiophosphate in 3 cc. sterile saline) and incubated for forty-eight hours. Unstained. This cell is said to be in early prophase.

FIG. 61. Strip radioautograph (Ilford) of Figure 60. The outline of the cell and the position of the nucleolus are drawn in. The radioautographic reaction indicates an appreciable concentration of P^{32} in the cytoplasm and none in the nucleolus. (Fig. 60–61 from Pelc and Spear, 1949.)

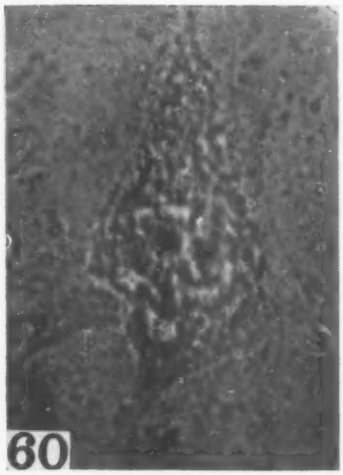
FIG. 62. Photomicrograph of the tongue of a rat injected with 200 μc. P^{32} carrier-free and sacrificed two hours after injection. Hematoxylin and eosin stain. ×ca. 100.

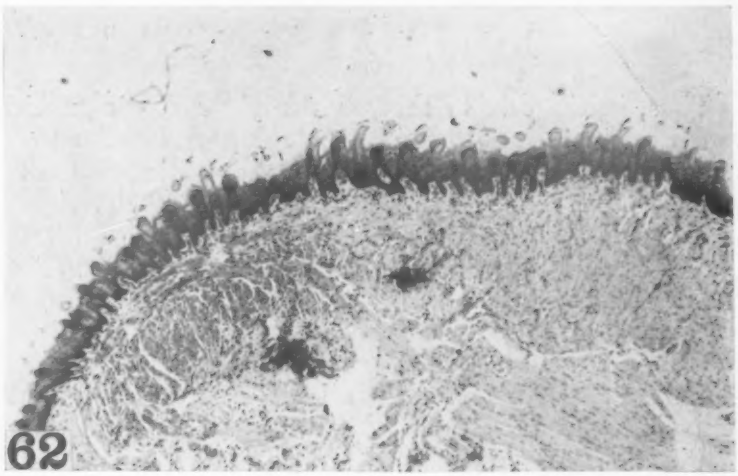
FIG. 63. Coated radioautograph (E.K. medium lantern slide emulsion) of section of rat tongue (serial section in Fig. 62) injected with 200 μc. of carrier-free radiophosphate, and sacrificed two hours after injection. The histological section was treated with ribonuclease. Unstained. ×ca. 100. The radioautographic reactions are mostly due to acid soluble phosphate, since inorganic and ribonucleic acid phosphate were removed by the histological procedure and desoxyribonucleic acid and protein incorporation of radiophosphorus was relatively small. Both the epithelium and the striated muscle show a reaction. (Fig. 62–63 from Stevens and Leblond.[91])

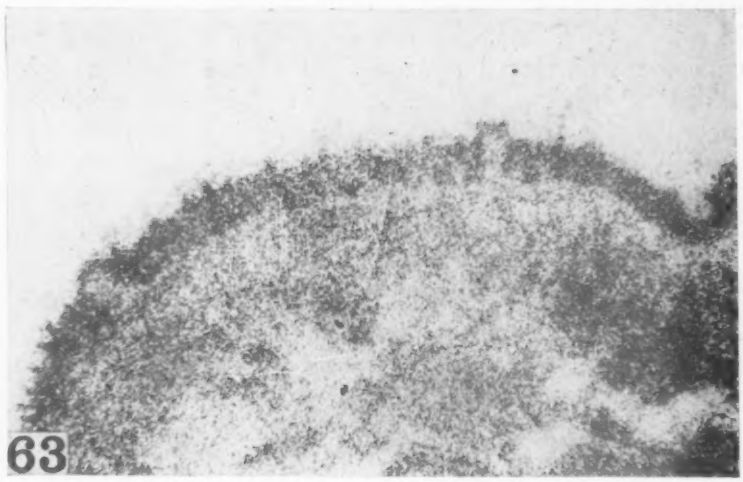
FIG. 64. Section of skin from pig exposed to mustard gas containing radiosulphur and killed twenty-four hours after exposure. Hematoxylin and eosin stain.

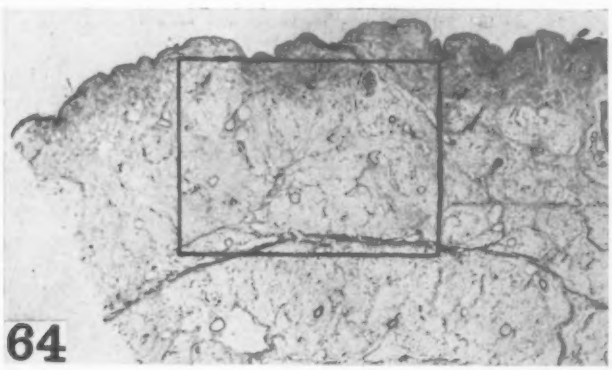
FIG. 65. Contact radioautograph of Figure 64. The radioautographic reaction indicates the accumulation of mustard gas predominantly in the epidermis and dermis where it infiltrates along connective tissue septa. (Fig. 64–65 from Axelrod and Hamilton.[3])

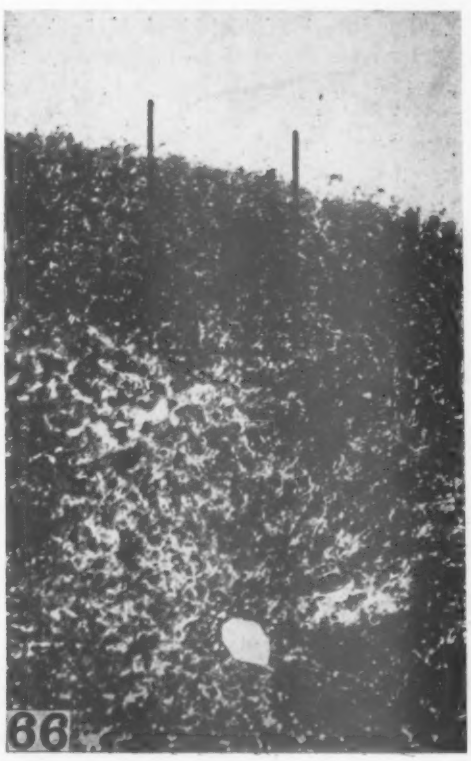
FIG. 66. Inverted radioautograph (E.K. Type M stripping film) of rabbit liver incubated for two hours in vitro with C^{14} labeled sodium bicarbonate in the presence of pyruvate substrate. Hematoxylin and eosin stain. ×110. The black granules predominate at the periphery of the lobule. (Fig. 66 from McDonald, Cobb and Solomon.[62])











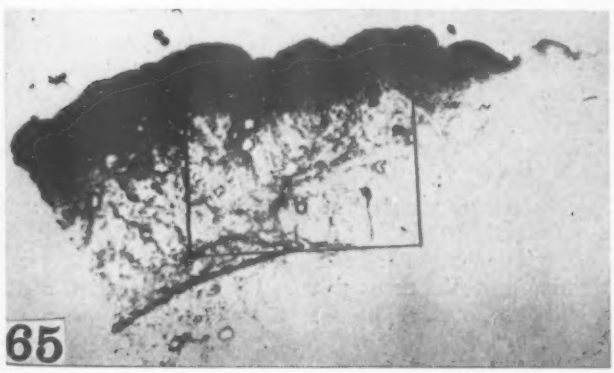


PLATE 5. (See facing page for legends.)

Thus, in the case of the *proteins of the nucleus*, it was found possible[59] to remove almost all the phosphorus containing compounds of the tissue other than desoxyribonucleic acid and perhaps some nuclear phosphoprotein (by fixation in formalin, or better, Carnoy fluid, deparaffination, and ribonuclease treatment). Radioactivity was thus found in tissues showing a rapid rate of mitotic division, such as lymphatic tissue, the granulosa cells of some of the ovarian follicles and, soon after injection, the crypts of Lieberkühn of the small intestine (Fig. 67). As the cells of the crypts are displaced up the sides of the villi, the nuclei, which are now labeled by incorporation of radiophosphate during mitosis, move toward the lumen as may be seen in a preparation obtained twenty-four hours after injection of the isotope (Fig. 68). This is an example of the use of the method not only for the purpose of investigating nucleic acid formation but also as a labeling technique for individual cells, since it supplies the first direct demonstration of the displacement of the cells of the intestinal epithelium in the living animal. Recently, Pelc (private communication) obtained reactions over individual chromosomes using P^{32} in germinating beans.

Similarly, *glycine* labeled with radiocarbon was found to be incorporated in liver proteins and in white blood cells, presumably in the nuclei of the latter,[16] as may be seen in Figures 70 and 71, which show the radioautographs of a lymphocyte and a polymorphonuclear leukocyte respectively. The percentage of cells giving a radioautograph varied with the cell type. This variation could be used as a rough index of the rates of formation of the various cells. In the same preparations, a few of the erythrocytes present were radioactive (Fig. 69) due to the incorporation

PLATE 6

FIG. 67. Coated radioautograph (E.K. medium lantern slide emulsion) of the duodenum of a rat injected with 2.4 mc. of nearly carrier-free radiophosphate and sacrificed two hours after injection. Ribonuclease treatment. Hematoxylin and eosin stain. ×125. An intense reaction is located over the crypts of Lieberkühn.

FIG. 68. Coated radioautograph of the duodenum of a rat injected with 2.4 mc. of nearly carrier-free radiophosphatase and treated as Figure 67. ×125. An intense reaction is located over the nuclei in the epithelium of the villi up to two-thirds of their height. Compare with Figure 67. (Fig. 67–68 from Leblond, Stevens and Bogoroch.[59])

FIG. 69. Mounted radioautograph (E.K. NTB emulsion) of an erythrocyte from the venous blood of a rat given three intraperitoneal injections of 1 μc. of radiocarbon labeled glycine. Blood was withdrawn twenty-five hours after injections, smeared and stained with Wright's stain. ×950. The presence of a radioautographic reaction over the erythrocyte indicates the incorporation of glycine in the course of its formation.

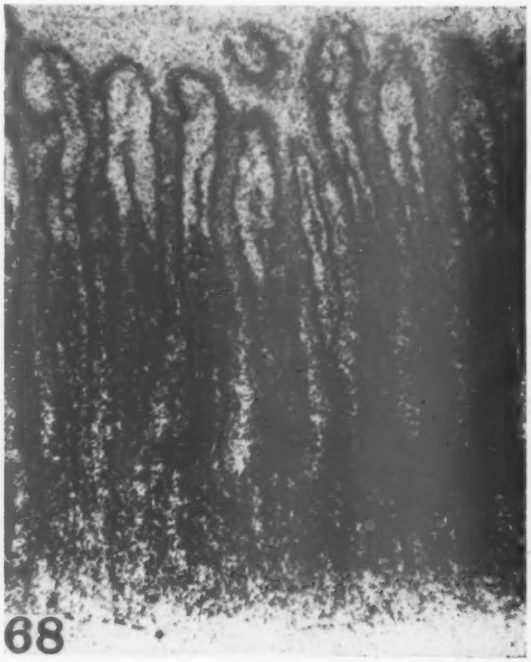
FIG. 70. Mounted radioautograph of a lymphocyte prepared as in Figure 69. ×950. Glycine is incorporated in the proteins of the lymphocyte.

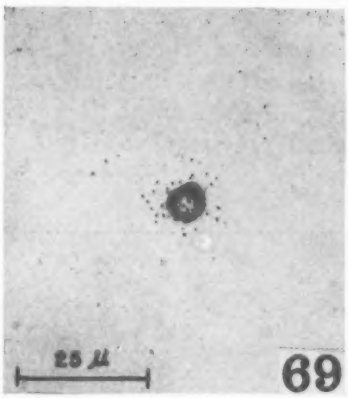
FIG. 71. Mounted radioautograph of polymorphonuclear leukocyte prepared as in Figure 69. ×950. Glycine is incorporated in the proteins of this leukocyte. (Fig. 69–71 from Boyd, Casarett, Altman, Noonan and Salomon.[16])

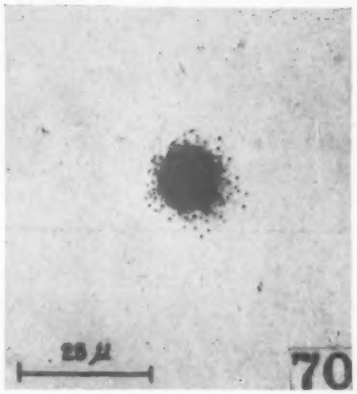
FIG. 72. Mounted radioautograph of a bronchus from a sensitized pig injected intravenously with about 8 mg. of radioiodine labeled bovine gamma globulin which caused death from anaphylactic shock in about five minutes. Harris hematoxylin. ×50. The large blood vessel at left is filled with antigen. Antigen is also seen concentrated in the fibrous tissue around the bronchus. The smooth muscle immediately beneath the mucosa is conspicuously lacking in activity. (Fig. 72 from Warren and Dixon.[96])

FIG. 73. Contact radioautograph (Ansco x-ray no screen film) of a kidney from a mouse injected with about 17 μc. of radioiodinated globulin fraction of anti-mouse kidney serum. The animal was sacrificed five days after injection. Punctate radioautographic reactions are visible. These were attributed to an accumulation of the material in the glomeruli of the kidney cortex, where presumably specific antibodies are present.

FIG. 74. Contact radioautograph (Ansco no screen x-ray film) of a kidney from a mouse injected with 17 μc. of radioiodinated globulin fraction of anti-mouse plasma serum and sacrificed five hours after injection. A diffuse radioautographic reaction is present throughout the tissue presumably due to content of the plasma in kidney. (Fig. 73–74 from Pressman, Hill and Foote.[79])







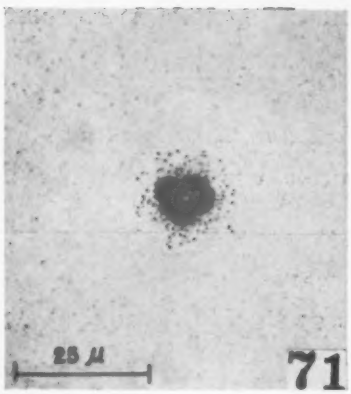


Plate 6. (See facing page for legends.)

of glycine into the hemoglobin molecule. That fewer erythrocytes than leukocytes were radioactive indicated a slower rate of formation of the former.

In the study of the *antigen-antibody reaction*, Warren and Dixon[96] used iodinated plasma globulin as an antigen to which guinea pigs were sensitized. Using this antigen iodinated with labeled iodine, these workers produced anaphylaxis and were able to show that radioactivity presumably due to the antigen-antibody combination occurred in the edematous connective tissue of the wall of the bronchi, and not in the muscle (Fig. 72). Similarly, anti-mouse kidney serum containing radioiodine was found to locate in the glomeruli of the kidney (Fig. 73), while iodinated anti-mouse plasma serum gave only a diffuse localization (Fig. 74) in the same organ,[79] thus indicating that the glomeruli were the site of a specific antibody-antigen combination.

Thyroglobulin. The entry of iodine into the thyroid has been the subject of more radioautographic studies than any other process occurring in the body. This is probably due to a combination of two circumstances: (1) the ability of the thyroid gland to concentrate iodine some thousand fold over the rest of the body, and (2) the rapid incorporation of this iodine into the protein, thyroglobulin. The high concentration of radioiodine in this readily retained molecule made it easy to radioautograph. Hence the broad application of the technique to both physiological and pathological studies, as was already apparent in the previously reviewed work on the subject.[42]

That thyroglobulin formed from radioiodine was the substance responsible for the radioautographic reactions was demonstrated by parallel biochemical and radioautographic studies.[58] The incorporation of injected radioiodide into the protein molecule occurred in the apex of the thyroid cell as indicated by the location of the radioactivity soon after injection (Fig. 75). At a later time interval, the radioactivity was diffused throughout the lumen of the follicle (Fig. 76), indicating the deposition of thyroglobulin into the thyroid colloid. In highly stimulated thyroids, as may be

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Plate 7

Fig. 75. Coated radioautograph (E.K. medium lantern slide emulsion) of a section of thyroid from a rat on a high iodine diet (22 μg. daily), injected with 20 μc. of carrier-free radioiodide and killed one hour after injection. Hematoxylin and eosin stain. ×600. The radioiodine is indicated by the black granules in the apical portions of the cells. Note the extent of background fog in the upper left corner.

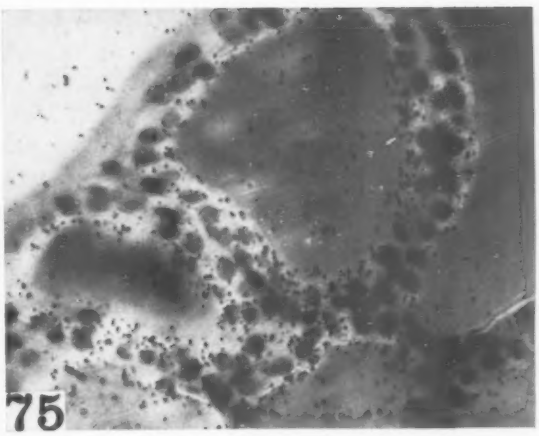
Fig. 76. Coated radioautograph as in Figure 75 except that the animal was sacrificed twenty-four hours after injection. Hematoxylin and eosin stain. ×600. The radioiodine is now located throughout the colloid.

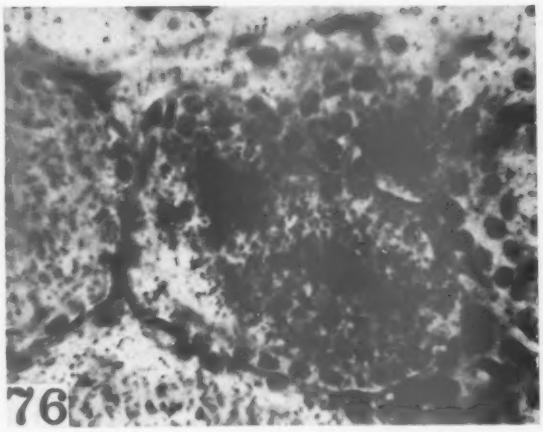
Fig. 77. Coated radioautograph (E.K. medium lantern slide emulsion) of a section of thyroid from a rat on a iodine deficient diet, injected with 20 μc. carrier-free radioiodide and sacrificed one hour after injection. H-E stain. ×400. The radioiodine is concentrated evenly throughout the colloid. Only granules of background fog can be detected in the cells. This indicates the very rapid secretion of thyroglobulin from the cells into the colloid. Compare with Figure 75. ×400. (Fig. 75–77 from Leblond and Gross.[58])

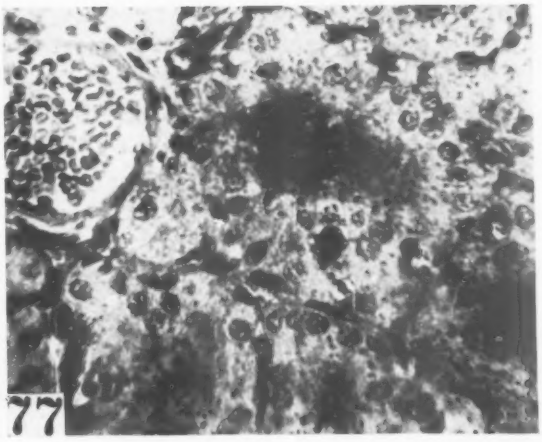
Fig. 78. Coated radioautograph of sections of organs (kidney, spleen, liver, pancreas, ovary and cross section of ventricules of the heart; the pituitary may be found between the kidney and the liver) from a rat injected with 100 μc. of radioiodide and sacrificed forty-eight hours after injection. Unstained. ×4. The reactions are believed to be at least in part due to the radiothyroxine formed from radioiodine by the thyroid. The strongest reaction is found in the liver and kidney. The remaining tissues show a diffuse concentration throughout their parenchymas. In the kidney most of the reaction is confined to the cortex while the medulla shows a lighter diffuse reaction.

Fig. 79. Photomicrograph of a section of undifferentiated embryonal adenoma of a thyroid from a patient given an oral administration of radioiodine. Hematoxylin and eosin stain.

Fig. 80. Contact radioautograph of Figure 79. The absence of a radioautograph in the area of the adenoma indicates the lack of function of that adenoma. The areas of blackening coincide with the normal thyroid tissue. (Fig. 79 and 80 from Dobyns and Lennon.[26])







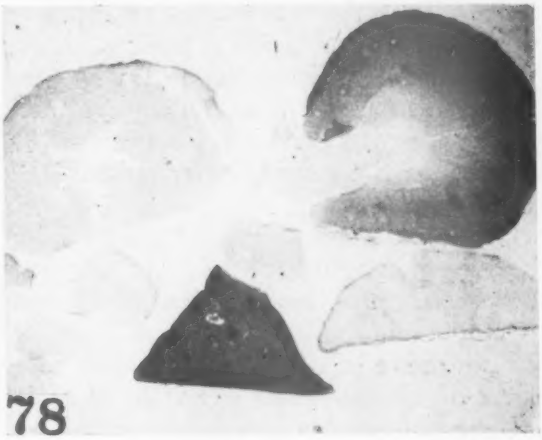


PLATE 7. (See facing page for legends.)

found in animals on a low iodine intake, the rate of deposition into the colloid was so rapid that the radioactivity appeared in the follicle lumen very soon after the injection (Fig. 77). Conversely, in a thyroid in which function is depressed, as in the hypophysectomized animal, the radioactivity in many of the follicles remained in the vicinity of the cell apex for a considerable time after radioiodide administration.[29,58] Thus, the rate of thyroglobulin formation could be estimated roughly by the location of the autographed radioiodine within the structure of the follicle. Later, the thyroglobulin is broken down by proteolysis into its amino-acid components; one component, thyroxine, passes from the colloid into the plasma to constitute the thyroid hormone.[44]

Thyroglobulin formation as shown by positive radioautographs of the thyroid after radioiodine injection has been used by Gorbman and co-workers to identify the beginning of thyroid activity in the course of embryological development.[42] In a recent paper, this author[40] was able to demonstrate that in the mouse the adult thyroid may contain structures derived from the ultimobranchial bodies. These structures do not take up radioiodine, in contrast with the normal medially derived thyroid tissue.

In clinical thyroid research the autographic detection of radiothyroglobulin has been extensively used in the study of thyroid neoplasms.[26,27,38,39,40,56,63,84,85,93] Dobyns and Lennon,[26] investigating nodular goiters, were able to correlate to a certain extent function with morphologic structure. Thus, they confirmed the previously observed fact[56] that the undifferentiated (embryonal) adenomas showed little or no ability to form thyroglobulin (Figs. 79 and 80), as was also the case with colloid nodules. In the hyperplastic adenomas they correlated cell height with function and were able to show that, while an increased mean cell height was common to all of these tumors, the incorporation of iodine into thyroglobulin was associated with a uniform increase in cell height, but where the cell height was more irregular, function diminished. Thus, in a papillary cystadenoma and papillary adenocarcinoma, both with extreme variability in cell height, no radiothyroglobulin was formed. The newer results in malignant adenomas may be summarized from the extensive paper of Fitzgerald and Foote.[38] The malignant adenomas, follicular and alveolar carcinomas showed some function and were most amenable to treatment with radioiodine. "Pure" papillary carcinoma did not fix radioiodine, although in the "mixed" type scattered areas might show some function. Similarly 7 of 8 typical solid carcinomas did not take up iodine in contrast to the mixed variety in which some uptake occurred. Except for rare focal areas in 3 out of 19 Hürthle cell carcinomas studied, no radioautographic reaction was obtained, as was also the case in the spindle cell, giant cell, and anaplastic types of tumors. In the study of the metastases, the ability to form thyroglobulin could be in some cases increased by thyrotrophin treatment or thyroidectomy (the effect of the latter being to increase the thyrotrophin secretion by the patients' own hypophyses).[85,93]

In the experimental control of therapy with radioiodine, radioautographic studies of function give some idea of the mechanism of destruction. Thus, in the rat[36] function was destroyed first in the central follicles of the gland which had been replaced by solid cell cords five days after radioiodine administration. This was also the case in areas where, although the follicular structure persisted, the colloid had been converted into a fibrinoid material. The follicles which retained their structure, retained the ability to form thyroglobulin.

In addition to following the formation of thyroglobulin in the thyroid, radioautography has permitted some promising preliminary results on the location of the thyroid hormone in the peripheral tissues. Allowing a sufficient interval for the conversion of injected radioiodide into thyroid

hormone, it has been possible to show a high concentration of radioactivity diffusely distributed throughout the liver, the cortex of the kidney and a lesser diffuse reaction throughout such organs as the heart, spleen, and pancreas (Fig. 78), while, in the adrenal the reaction was found to be somewhat stronger in the cortex than in the medulla. These findings agreed with some of the radioautographic data on thyroxine distribution obtained after the injection of labeled thyroxine.[43]

SUMMARY

The radioautographic method consists in approximating a section of a radioactive organ or tissue to a photographic emulsion on which the sites of radioactivity will be recorded.

A theoretical study was carried out to determine the conditions giving the most satisfactory radioautographic images. The results obtained are as follows: (1) The resolution of the image is best when the thicknesses of section and emulsion, and especially the space between the two, are reduced to a minimum. (2) The preparation should be underexposed to obtain densities as low as may be conveniently identified. (3) The emulsion used should contain a high concentration of small grains of fairly uniform size, and have a low background fog.

The technical details of the practical application of these principles using the available photographic materials have been described for the various methods currently in use, namely "contact," "mounting" and "coating" methods. The best preparations have been obtained by coating sections with dilute Eastman Kodak medium lantern slide emulsion (Fig. 19 and 75). These preparations consist of a 5 micron section and a 5 micron emulsion separated by a celloidin coating of not more than a fraction of a micron. Exposure was at low temperature. It is expected that, in the future, the "nuclear" emulsions containing a high concentration of grains of fairly uniform size (Ilford, Eastman Kodak) will be prepared in convenient form (not only in strip form but also in bulk form for coating) with sufficient sensitivity and freedom from fog to replace the available material.

A critical review of recent radioautographic work in this and other laboratories illustrates the results obtained with various methods of radioautography. It is emphasized that the technique includes the chemical characterization of the radioactive material in the sections, an indispensable step in the interpretation of the radioautographic image.

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SELF-HEALING EPITHELIOMA OF THE SKIN

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SELF-HEALING epithelioma of the skin is a condition in which cutaneous neoplasms develop from time to time, and, though histologically identical with well differentiated squamous carcinoma, show a tendency to spontaneous healing. In some cases this goes on for a long time so that all stages between new lesions and healed ones are seen, but in others the capacity for healing seems to become diminished after a time and may eventually be lost. The condition was first recorded by J. Ferguson Smith[2] in 1934, and since the condition has become known, more cases will probably be recognized. It may be that such patients are not so uncommon as was first thought and they are not only of great clinical interest but might even some day suggest a new approach to the cancer problem should the spontaneous process of healing become fully understood. It would therefore appear that those who encounter such cases should record them, and this paper presents the relevant history of such a patient and of certain members of his family. This patient was referred to me in 1943 but it was 1949 before the progress of those concerned had been followed sufficiently to permit of comment.

CASE REPORTS

J. G., male, aged sixty-nine, was referred to me by Professor Illingworth in March, 1943, for an opinion as to possible radiotherapy of an epithelioma on the perineal skin, situated just in front of the anus and to the right of the midline. The patient had been aware of the lesion for six months and, though obviously malignant and infiltrative, it looked warty and was judged on clinical grounds to be a neoplasm of high differentiation. It measured 5 by 3 cm. in size with well defined margins, but anteriorly rather indefinite induration extended upward towards the right inferior pubic ramus; this was rather tender and boggy giving a distinct suggestion of local sepsis. No glands could be felt in the groins. In view of the sepsis and tumor type, operation was advised. Excision was carried out by Professor Illingworth on April 5, 1943. The growth was easily removed and the fullness in front of it found to contain watery fluid and some small sloughs due to a subacute infective process. The parts healed rapidly in spite of the sepsis. Pathological examination of the specimen by Dr. McLetchie described the growth as

Fig. 1. Patient J. G., showing some of the more deeply pitted scars on the face.

a highly differentiated epithelioma associated with chronic inflammatory change, fibrosis, and regressive changes in the invading tumor.

In the course of investigation of the patient after admission, a number of scars, both level and deeply pitted, were observed on the forearms and face. It was then elicited that, since the age of twenty-three, the patient had suffered from growths on the skin which developed slowly and then healed with considerable scarring. Sometimes these scars were level but occasionally the lesion seemed to become demarcated and to fall out of the skin leaving a deep pit (Fig. 1). No treatment had ever been adopted for these lesions except as regards one on the right upper eyelid to which some caustic substance had been applied. At the time of this

examination, many scars were obvious on the face and forearms, but not elsewhere on the body, while, of active lesions, there were two on the right forearm and one near the left wrist. Clinically, these were obvious squamous epitheliomas and the most interesting was one of an irregular outline measuring some 3 cm. along its maximum axis (Fig. 2). The striking feature

Fig. 2. Squamous carcinoma of the skin of forearm (J. G.). The outline of the lesion is obvious and it can be seen that about half of the neoplasm has healed spontaneously. The scar in this case is flat.

of this lesion was that part of the area was an obvious epithelioma and part a flat healing scar. The photograph shown was taken on June 18, 1943, by which time the scarred and healing area had increased notably, and a strip of skin was excised by me in such a way that it

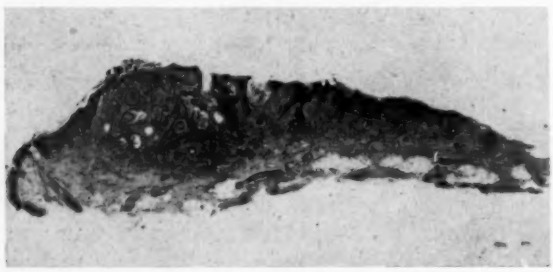

Fig. 3. Low power view of section cut through the lesion seen in Figure 2 showing both active and healed parts. ×4.

passed both through the tumor and the scarred area so as to demonstrate the process of transition. No attempt was made to excise the lesion and the process of healing was watched; it was complete by October, 1943. In August, 1944, two fresh lesions appeared on the ulnar aspect of the right wrist and the following April two more were seen on the left arm, by which time the others were all healed. After this the patient failed to attend, although many efforts were made to contact him, and eventually we found that he died in November, 1945, from rapid and extensive recurrence of the anal lesion.

Histopathological Examinations. The tumor excised from the perineum in April, 1943, was reported upon in the pathology department by Dr. N. G. B. McLetchie as detailed. The skin from the right forearm removed in June was reported upon by Dr. Marion K. Gilmour as a highly differentiated squamous epithelioma. This section was seen by the late Professor Shaw Dunn who thought that it came into the category of self-healing primary squamous carcinoma of skin. Examination of these sections

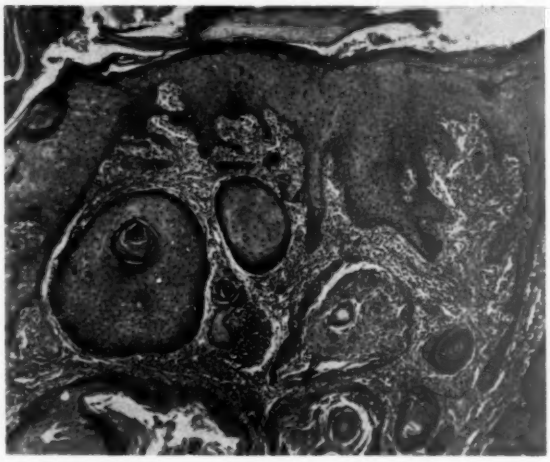

Fig. 4. Part of section shown in Figure 3 illustrating the well differentiated squamous carcinoma at the active end of the lesion. The tumor is definitely invasive and of highly differentiated type with well developed cell nests and considerable round cell infiltration. ×35.

reveals many interesting features. A good low power view of the whole area (Fig. 3) showed quite clearly the active epithelioma at one end and the rather atrophic healed skin at the other. A high magnification of the epitheliomatous part (Fig. 4) showed broad processes growing downward from the epidermis with definite invasion and the formation of cell nests containing much keratin. Few mitoses were seen and the general structure was of a highly differentiated tumor of definite malignancy. There was considerable round cell infiltration. The section showed what was probably a coalescence of cell nests and this had occurred in such a way that the surface epithelium appeared to be inverted at certain places, forming a crypt of some size containing much keratinous debris. Evidence of

this process at a less advanced stage could be seen elsewhere in the section.

Towards the inactive end of the lesion it was found that the epithelial down-growths became less and less in extent while still exciting a round cell response. Further on, only some fraying of epithelium could be seen at the tips of the processes. At the same time the cell nests gradually became less and less prominent until none could be made out (Fig. 5). The healed end of the section, previously seen clinically to be the seat of gross tumor growth, presented a rather atrophic epithelial covering beneath which were a few scattered clumps of round cells in a somewhat fibrous cutis.

Family History. The patient knew of no such lesions occurring in the case of his brothers or sisters or of his mother, but believes that his father had something of the same sort, though, owing to an early death, no exact details are available. Of the patient's five sons, however, three seemed to have been affected in the same way and they were asked to attend this department for investigation.

Peter G. (aged twenty-one), an apprentice printer, was in the late Professor Archibald Young's wards here in 1939 with an epithelioma about 3 cm. in diameter on the skin of the left thigh just above the knee. At the time of admission, it had been present for three months and there were some glands palpable in the groin. Mr. Leslie Orr operated on June 6, 1939, removing both glands and primary lesion with the connecting sheet of tissue. The pathological report by Dr. Janet Niven indicated no invasion of the glands; the primary lesion was described as a well differentiated epithelioma. There was a healed scar on the left leg just below the knee and this was said to have resulted from a similar ulcer which healed without treatment. When seen by me in September, 1946, this patient presented several pitted scars on the face and an excision scar on the nose, due to an operation carried out while he was a prisoner of war. In the cavum of the right ear was a small active lesion presenting the usual clinical features of low grade squamous malignancy. The patient was not troubled by his skin condition and he did not desire either to attend for observation or for any treatment, although the situation was explained to him.

Wm. G. (aged thirty-eight), a printer's assistant, was admitted to Mr. Hutton's wards in July, 1941, with an epithelioma of some two months' duration situated at the lateral border of the left eyebrow. It was about 2 cm. in diameter, and on July 21, 1941, Mr. Hutton excised it carrying out a plastic repair. No enlarged glands were detected. The pathological report by Dr. Janet Niven described the lesion as a well differentiated infected epithelioma; a biopsy prior to this operation had suggested a sessile papilloma which had undergone malignant change. The result of this operation was most satisfactory, but the patient, when seen in September, 1946, presented further lesions at the right angle of mouth, on the dorsum of nose and on the left ear. These did not seem to be healing and so treatment was given with a good result (85 kv., 5 ma., 1 mm. Al filter, 15 cm. focal skin distance, 100 r per minute, 4,000 r incident dose in two weeks: Dr. S. D. Scott Park).

A review of the case in January, 1949, showed that the treated areas remained inactive but that further lesions had developed on the face, right wrist, and left leg. Those on the extremities were evidently healing spontaneously and a biopsy of the one on the leg showed that the lesion was quiescent; the histopathological examination was carried out by Dr. J. A. Milne. On the other hand, the facial lesions appeared to be active and, in view of the encouraging result already obtained in this case, an attempt was made to deal with two of these new lesions. One between the eyebrows and one on the left ear were treated (140 kv., 5 ma.,

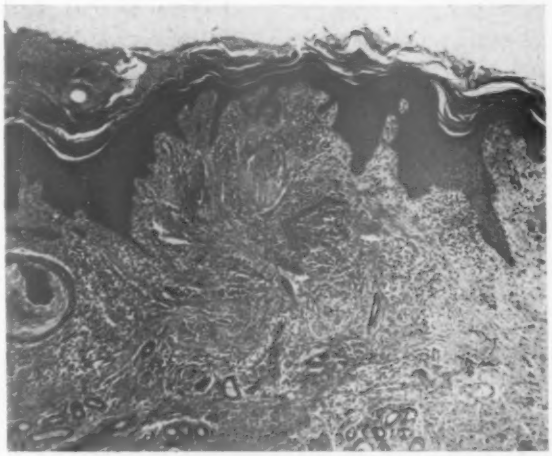

FIG. 5. Part of section shown in Figure 3 taken from the healed end of the lesion, showing fibrosis of the cutis with a rather thin and atrophic epidermis. There is still some round cell infiltration. ×35.

0.25 mm. Cu and 1 mm. Al filter, 15 cm. focal skin distance, 68 r per minute, incident dose 4,000 r in three weeks to each lesion). As it was felt impracticable to carry out radiotherapeutic treatment to more and more areas, the case was eventually referred in March to Mr. J. Scott Tough's Plastic Unit at Ballochmyle Hospital, Ayrshire.

Thomas G. (aged twenty-nine), apprentice engineer. This patient first began to experience

Fig. 6. Patient Thomas G., showing posterior aspect of left ear. The larger lesion is obviously of very highly differentiated type, the two smaller ones being more infiltrative.

Fig. 7. Patient Thomas G. Outer aspect of right ear showing a number of small infiltrative lesions. Note the scars on the cheek.

serious trouble with growths on the skin when he was a prisoner of war in Germany in 1941, but, when he came to this department in October, 1946, it was obvious that lesions had been present to some extent for years and, after being questioned, the patient thought the first appearances might have been about sixteen years previously. In this case the tumors were widespread and extensive. The regions most affected by active lesions were both ears and the chin, where the lesion was of a rather unusual type. The left ear (Fig. 6 and 7) presented posteriorly two small lesions and one 3 cm. in diameter, while the anterior surface showed several healed scars; both aspects of the right ear showed a larger number of small lesions. The chin (Fig. 8) was the seat of a growth measuring 2 by 2.5 cm. with a smaller lesion to its right side and the photograph shows that many pitted scars are present on the face; the defect in the skin of the nose is the result of an operation carried out in the prisoner of war camp. Histopathological examinations were carried out on tissue from a representative lesion

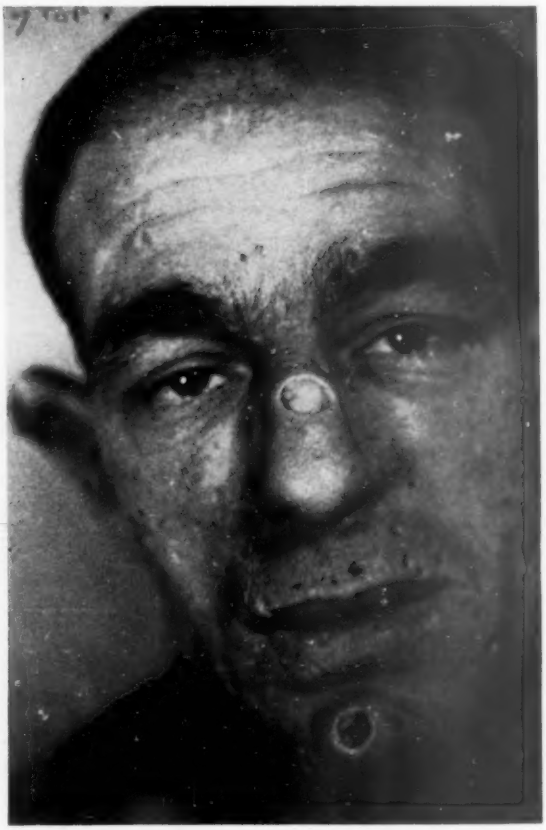

Fig. 8. Patient Thomas G. View of the face showing many healed and pitted scars. Defect on the nose is the result of operative interference as explained, and the rather unusual lesion on the chin was found to be a sebaceous adenoma.

on the right ear and from the rather unusual one on the chin. The former specimen showed highly differentiated epithelioma with degenerated and in some instances calcified cell nests, together with an extreme degree of cellular infiltration, but the latter showed only an excessive development of sebaceous glands and hair follicles. The histopathological examination was carried out by Dr. Janet Niven. The size and activity of the lesions seemed to indicate that some treatment should be adopted, except for the peculiar one on the chin, since healing was not taking place. Treatment was given to each ear in October, 1946 (200 kv., 8 ma., 0.5 mm. Cu and 1 mm. Al filter, 50 cm. focal skin distances, 25 r per minute, 4,000 r in three weeks: Dr. S. D. Scott Park). Unfortunately there was not the response which one would have expected in the case of an ordinary skin epithelioma but the condition remained fairly static until January, 1949, when the patient was referred to Mr. J. Scott Tough's Plastic Unit.

DISCUSSION

Cases of the type described above have been recorded before, the first published description being by Smith[2] in 1934. Later in the same year another case was described by Dunn and Smith.[1] The first of these was a young man with multiple cutaneous lesions showing spontaneous healing of many and presenting no metastases after seven and a half years; this patient died comparatively recently of another condition.[3] The second case was an older patient who had a single tumor excised from the skin of the thigh, and the histopathological features recorded include changes similar to those described in the case of the patient J. G. who showed such remarkable tendency to regression of the lesions. The histological preparations from this patient (J.G.) demonstrate not only the neoplastic character of one of the lesions but also the process of spontaneous healing (Fig. 3). Capacity for healing was obvious in all our patients for a certain time, as evidenced by the many scars, but it failed eventually in the case of the parent, and was feeble or absent in the case of the sons by the time they came under observation. It will be noted that almost all the lesions appear on the exposed surface of the body but there is no obvious physical or occupational cause to account for this, except for the possibility that normal ultraviolet radiation may play some part.

All who deal with malignant tumors are aware of the very different grades of biological activity met with even in one class, as is well shown in the case of carcinoma of tongue, and they would probably agree that the body mechanisms of defense and healing play a part in modifying the course of tumor growth. This is seen to an exaggerated degree in such cases as have been described and so it is suggested that a more intimate study of these patients might ultimately be of great value. Increasing knowledge of defense and healing processes might carry with it possibilities of their artificial stimulation and it is conceivable that this might be of value in the therapeutic field. The biological grade encountered here has always been that of an "adult" type of tumor, the appearance both clinically and histopathologically giving the picture of a highly differentiated lesion. The main practical comment one might make at the moment is that this condition should be borne in mind by all who have the chance of seeing skin malignancy, and that radiotherapy, in this series at least, seems to have been of limited value. It was only adopted where some interference seemed inevitable and it is probable that surgical measures will prove more helpful, although any method of treatment is bound to present difficulties owing to the awkward distribution of the lesions and the possibility of new ones appearing.

Finally, it is of interest to note that since the foregoing account was written we have seen in this department one more definite case of self-healing epithelioma and also a family of which three members are probably affected. None of these patients has been studied for a long enough time, to make any comment possible.

I am indebted to Professor Illingworth for permission to give details of the case upon which he operated, and to the various members of the staff of the Pathology Department of the Western Infirmary and University of Glasgow who examined the routine pathological specimens.

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EFFECT OF PHYSICAL AND CHEMICAL FACTORS ON PHAGOCYTOSIS IN THE PRESENCE OF IRRADIATED HUMAN BLOOD AND PLASMA*

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THE influence of various sera and fluid media on phagocytosis has been studied extensively since the initial investigations of Metchnikoff.[23] Between 1902 and 1904 Wright and Douglas[32] set up a technique for quantitative studies on immune sera intensifying the phagocytic properties of leukocytes.

Investigations on different physical and chemical factors affecting directly or indirectly phagocytosis through the fluid media widened greatly the scope of immunology. For example, Cowie and Chapin,[3] using the technique of Wright, demonstrated the presence of a thermolabile substance in normal human serum which intensified phagocytosis even in dilutions of 1/15. This substance, which lost its effectiveness by heating for ten minutes at 60° C. was thought to be a thermolabile opsonin. On the basis of Ehrlich's theory, opsonins were considered to belong to that group of antibodies which had a double amboceptor-complement structure, like the hemolysins and the bacteriolysins. Sleeswijk[29] demonstrated a thermostable substance in the serum, lymph and peritoneal exudate, which he classified as an agglutinin in contrast to the thermolabile substance which opsonized the cocci by enveloping them.

Between 1915 and 1920 the investigations of Hektoen[11,12,13] on immunological processes in rats, dogs and rabbits exposed to various doses of roentgen rays at the time of injection of antigen, showed a reduction of antibody production. This, he thought, was due to the injurious effect of roentgen rays on the lymphoid tissue. But most probably the doses used were about or over 300 r as measurements were based on the effect of roentgen rays on the white blood cell count. Recently, Craddock, and Lawrence,[4] using 250 r for whole body irradiation of rabbits, elicited a transient depression in antibody production. Simonds and Jones[28] showed that repeated small doses did not affect opsonin production. On the other hand, various other histopathological studies on induced bacterial inflammations subjected to small doses of roentgen rays qualitatively showed an increase in phagocytosis. Thus, in a general review on the action of roentgen rays, in 1928 Domagk[5] states that small doses stimulate the production of antibodies. In 1942 Bisgard, Hunt, Neely and Scott,[2] irradiating with 100 r the abdomen of rats or rabbits, twenty-four to forty-eight hours prior to intraperitoneal injection with lethal amounts of *E. coli* reduced the mortality rate from 100 per cent to 50 per cent. This is attributed to an antitoxic agent liberated into the peritoneal cavity possibly from cells damaged by roentgen rays. Between 1942 and 1944 quantitative studies by Rosselet and Sarian[26] showed that doses ranging from 75 r to 150 r intensified the phagocytic properties of normal human blood two to four times, while doses exceeding 200 r caused a reduction. Recently, Glenn[8,9] demonstrated an augmentation of phagocytosis of *S. aureus* in rabbits irradiated with 100 r twenty-four to forty-eight hours prior to inoculation. More recently, Sarian[27] showed that even 15 r as absorbed in 10 cc. of normal human blood or plasma causes a significant rise in the opsonic index. Since there could also be demonstrated a certain

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specificity of the augmented antibodies, the inference was that small doses of roentgen rays cause an activation of the already present opsonins of normal human plasma and probably some new production through a rearrangement of the electronic distribution on the surface of the immunologically inert protein molecules.

In the following experiments, a few physical and chemical factors were controlled and studied as to their bearing on phagocytosis in both irradiated and non-irradiated normal human blood and plasma.

EXPERIMENTAL PROCEDURE

One-tenth cubic centimeter portions of a suspension of *S. aureus* from a twenty-four hour culture (5 million bacteria per cubic millimeter of physiological saline) was mixed with 0.1 cc. portions of either whole blood or a suspension of leukocytes (5,000 per cu. mm. of physiological saline) in small Kahn tubes to which were added 0.1 cc. portions of various plasma and fluids to be tested. These tubes were stoppered, sealed (with paraffin) and incubated at 37° C. for thirty minutes, being shaken gently. Smears were made from the content of each tube and after staining with Giemsa (1/10 dilution) the average number of bacteria engulfed per leukocyte (*phagocytic power*) was determined by counting the number of bacteria in fifty consecutive leukocytes visualized. Dividing the phagocytic power of an experimental sample by that of the control, one obtains the *phagocytic index* (opsonic index).

Plasma was prepared by collecting the supernatant fluid after centrifugation (for fifteen minutes at 2,500 rev./min.) of citrated or partially defibrinated blood. The suspension of leukocytes (5,000 per cu. mm. of physiological saline) was obtained from the residual cellular elements of blood by double washing with physiological saline and centrifugation.

The factors of irradiation, unless otherwise stated, were: 100 kv., 15 ma., no filter (inherent filtration equivalent to 0.3 mm. Cu), 40 cm. target-blood surface distance. The intensity of radiation was 10 r/min. (with backscatter). Ten cubic centimeter samples of citrated or partially defibrinated blood and of plasma were irradiated in flat bottomed, round glass dishes of 20 sq. cm. surface exposure.

1. *Effect of anticoagulation measures on phagocytosis of irradiated and non-irradiated blood and plasma.* Normal human blood was mixed with a sterile A.C.D. solution of the Abbot Laboratories (dextrose 2.45 per cent + sodium citrate 2.2 per cent = citric acid 0.8 per cent) to the ratio of 4 volumes to 1. Samples of this citrated blood and the plasma obtained from it were irradiated with 50 r and 100 r. The same was done with blood partially defibrinated (by glass beads) and plasma obtained from it. The phagocytic powers of citrated and partially defibrinated blood were compared both as to the controls and the irradiated samples. Similarly, the phagocytic powers of non-irradiated leukocytes (from a suspension in physiological saline of a concentration of 5,000 leukocytes per cu. mm.) mixed with plasma obtained from citrated blood irradiated with 50 r and 100 r were compared with those mixed with plasma obtained from partially defibrinated blood irradiated with 50 r and 100 r. The same comparative studies were made after heating at 65° C. for fifteen minutes samples of plasma obtained after irradiation of citrated and partially defibrinated blood. Also samples of plasma, obtained from citrated and partially defibrinated blood respectively, after being irradiated with 100 r, were studied comparatively as to phagocytosis both before and after heating at 65° C. for fifteen minutes.

On the average, there was a 35 per cent loss in the phagocytic power of leukocytes due to citration (as compared to partial defibrination). This loss was statistically significant (Fig. 1).

Further studies were made where partially defibrinated blood was mixed with A.C.D. solution to the ratio of 4 to 1 volumes respectively. The results, as recorded in summary in Figure 2, showed a more

important drop in phagocytosis, due probably to the additional traumatization of leukocytes by the glass beads during the process of defibrination.

In trying to explain this drop, pH measurements of the various samples of blood and plasma were made. Defibrinated blood showed a slightly alkaline pH 7.6 while the citrated blood had pH 6.6 (Beckman pH-meter). After irradiation (200 r to 15 cc. of blood) defibrinated blood had pH 7.8 and citrated blood pH 6.8.

The neutrality of pH has been found to be optimal for phagocytosis. The work of Menkin[19] stresses the deleterious effects of an increase of acidity on phagocytosis. The citrated blood being on the acid side (pH 6.6) this may explain to a certain degree the fall in phagocytosis. According to the

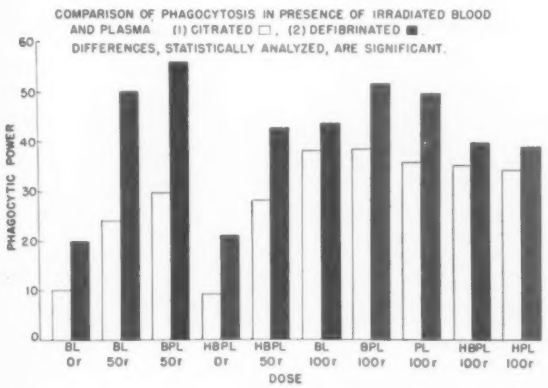

Fig. 1. Abbreviations explanatory of the figures:
BL 50 r = Blood irradiated with 50 r
BPL 50 r = Plasma obtained from blood irradiated with 50 r.
PL 100 r = Plasma irradiated with 100 r.
HBPL 100 r = Plasma obtained from blood irradiated with 100 r and then heated for 15 minutes at 65° C.
B(S) = Blood stored for 48 hours at 0° C.

investigations of Allgöwer,[1] even small doses of sodium citrate greatly handicap phagocytosis.

In this discussion it should be pointed out that other chemical factors also can affect phagocytosis. Thus, Ouweleen[25] found 0.6 to 0.5 per cent of sodium chloride as being optimal for phagocytosis. According to Kanai[16] calcium ions increase the rate of phagocytosis and 0.02 per cent calcium chloride is an optimal concentration. Tunnicliff,[31] injecting rabbits intravenously with calcium gluconate, calcium chloride, sodium salicylate, sodium iodide, dextrose

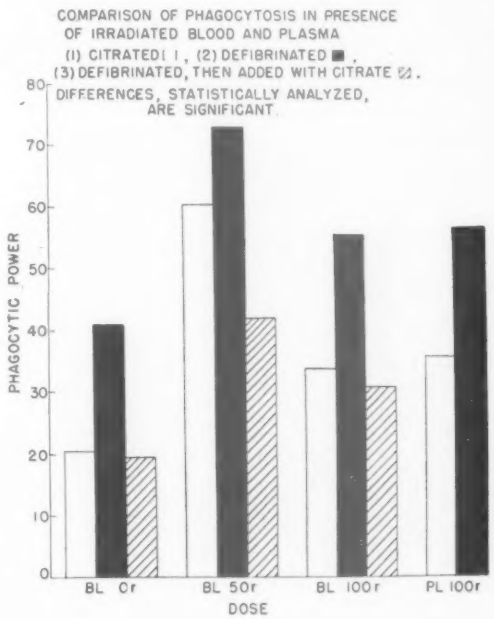

Fig. 2

and neosalvarsan, could demonstrate marked increase in phagocytosis. In vitro, dilute solutions of calcium gluconate, sodium iodide, dextrose and mercurochrome in dextrose stimulated phagocytosis. Menkin[20] states that fat soluble substances (as iodoform, chloral hydrate, ethyl alcohol) or low concentrations of chloroform increase phagocytosis. Histamine augments phagocytosis in a concentration of about 1:40,000. Messina and Verga,[22] using citrated blood and a suspension of virulent *E. typhosa* found that vitamin C raises the opsonic power of plasma.

2. *Effect on phagocytosis of storage of irradiated blood and plasma* is summarized graphically in Figures 3 and 4. Irradiated blood and plasma as well as non-irradiated (control) samples were stored for forty-eight hours at 0° C. and phagocytic studies carried on subsequently. It was found that such a storage does not destroy the in-

creased phagocytosis enhancing properties of irradiated blood and plasma. In fact, there is a slight increase in both the controls (non-irradiated) and the irradiated samples. Hence the opsonic indices of irradiated and stored samples do not show a rise (Fig. 4).

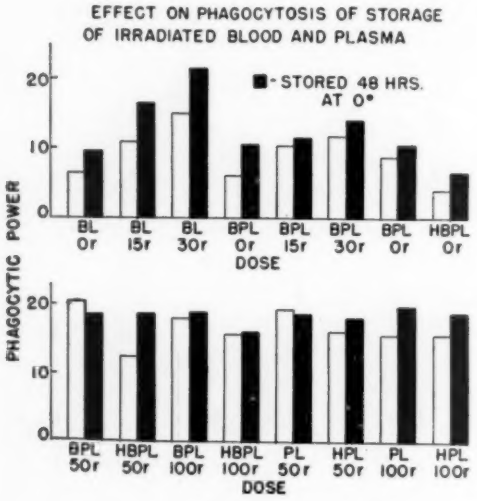

Fig. 3

This increase in the phagocytic power of blood (irradiated or non-irradiated) due to storing was small enough as to be statistically non-significant in about two-thirds of the series of experiments. However, since this slight increase was a constant finding it would be interesting to explain it on the basis of liberation of antibodies by the disrupting white blood cells. In fact the number of lymphocytes decreased after storing blood for forty-eight hours at 0° C. Thus, on the basis of the work of Dougherty *et al.*[6,7] it could be assumed that the augmented number of broken down lymphocytes due to storing would release more *gamma* globulin and antibodies and hence intensify phagocytosis.

There could not be demonstrated any phagocytosis in lymphocytes. The phagocytic power of basophiles, eosinophiles and monocytes was much lower than that of neutrophiles. Neutrophiles with intense phagocytosis showed the greatest number of disrupted cells. These disrupted neutrophiles would help the over-all process of phagocytosis through the partial or total killing of the ingested bacteria and most probably through the liberations of enzymes and antibodies on their breakdown (Opie,[24] Jochmann,[15] Jobling and Petersen,[14] Menkin,[21] Bisgard *et al.*[2]). However, these disrupted phagocytes were counted as leukocytes with zero phagocytosis

3. *Phagocytosis and the effect of heating irradiated plasma.* Non-irradiated and irradiated plasma as well as plasma obtained from irradiated blood were heated (in a water bath) for 15 minutes at 65° C. These were mixed with normal leukocytes (suspended in physiological saline) and phagocytic studies performed. The results are presented in summary in Figure 5. The antibodies or opsonins produced or activated by small dose roentgen irradiation are thermostable in nature. However, there is a slight decrease in the phagocytosis-inducing properties of plasma. This decrease, although non-significant (when analyzed statistically), is yet constant. It could be accounted for by the inactivation through heating of the thermolabile components of the antibodies (the thermolabile opsonins of Cowie and Chapin,[3] for example). This assumption gets further support from the

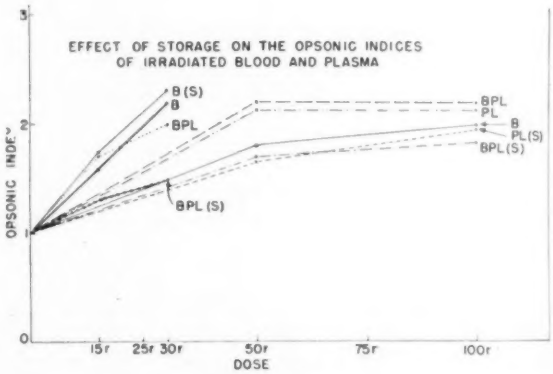

Fig. 4

fact that the amount of the decrease in phagocytosis due to heating is nearly the same for both the non-irradiated and irradiated samples. On the other hand, Ledingham[17] and more particularly Madsen

and Wulff[18] have demonstrated that the optimal temperature for phagocytosis by normal human leukocytes is 37° C.

As to the nature of this thermostable antibody produced or activated in the blood and plasma by small doses of roentgen rays, it could be surmised that partly it may be the activated thermostable agglutinin demonstrated by Sleeswijk.[29] However, the investigations presented here and previously[27] tend to point towards specific opsonins as comprising the more important part of this thermostable substance brought out by irradiation.

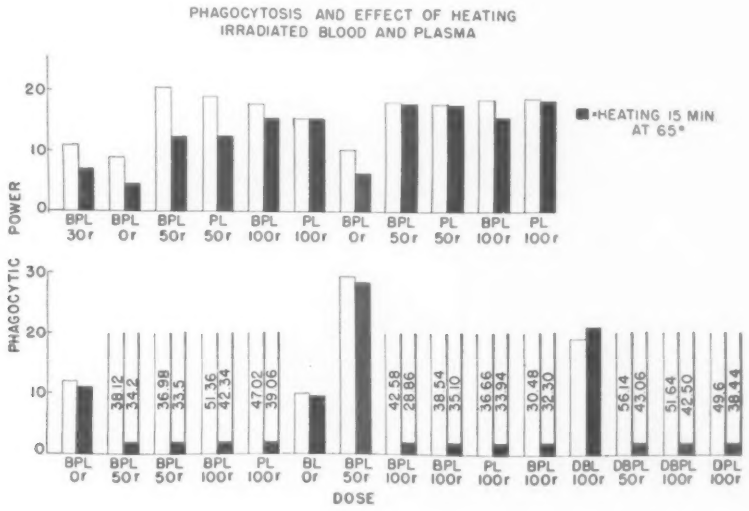

Fig. 5

4. *Phagocytosis and slight variation in the quality of rays.* Slight variations in the quality of rays did not cause an appreciable difference as to the degree of intensification of phagocytosis (Fig. 6). This may be explained by the fact that the range of wavelength variation is a small one. Thus, in previous investigations (Rosselet and Sarian[26]), when the variation in the quality of rays was more important, the softer rays proved to be more potent in intensifying phagocytosis. This may be due to more ion pair formation by softer rays (Gray[10]). Also, the ionization electrons of high voltage roentgen rays being more penetrating are less effective biologically (Trump[30]) as the depth of the irradiated blood or plasma samples did not exceed 5 mm. Thus, there is reason to think that the rate of phagocytosis enhancement due to roentgen rays is dependent to a certain degree on the production of an optimal ion density per gram of irradiated blood or plasma. The following series of experiments on the dilution of roentgen-ray dose will help further to elucidate this hypothesis.

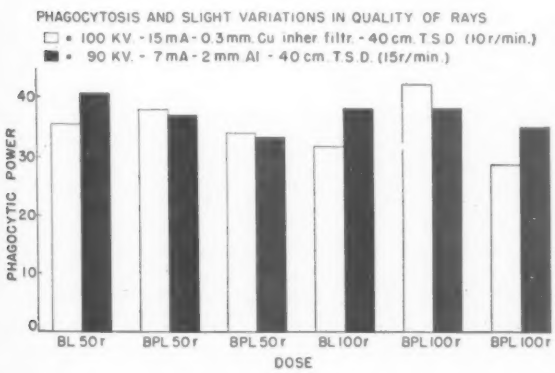
PHAGOCYTOSIS AND SLIGHT VARIATIONS IN QUALITY OF RAYS
100 KV. - 15 mA - 0.3 mm. Cu inher. filtr. - 40 cm. T.S.D. (10r/min.)
90 KV. - 7 mA - 2 mm. Al - 40 cm. T.S.D. (15r/min.)
PHAGOCYTIC POWER
BL 50r
BPL 50r
BPL 50r
BL 100r
BPL 100r
BPL 100r
DOSE

Fig. 6

5. *Phagocytosis and dilution of roentgen-ray dose.* Irradiating with 100 r 10 cc. and 20 cc. amounts of blood respectively there was demonstrated a small decrease in phagocytosis. This decrease due to diluting the roentgen-ray dose twice was statistically

significant in about two-thirds of the experiments. Comparable results were obtained by using non-irradiated leukocytes mixed with plasma obtained from 10 and 20 cc. samples of blood irradiated with 100 r. Thus the roentgen-ray dose was diluted twice but its physiological effect decreased by approximately 10 per cent on the average (Fig. 7).

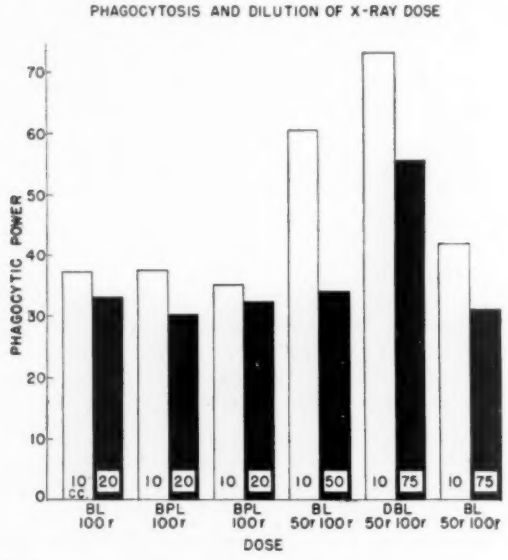

Fig. 7

Irradiating 10 cc. of blood with 50 r and 75 cc. with 100 r was comparable to diluting 3.75 times the roentgen dose. Then the decrease in the enhancement of phagocytosis was approximately 25 per cent on the average (Fig. 7) and significant statistically. In one experiment, diluting the roentgen dose 2.5 times, the relative fall was 40 per cent approximately. These dilution experiments are not complete and no mathematical considerations could be determined as yet. Thus, curves of physiological effectiveness of roentgen rays plotted against a gradation of increasing volume of blood or plasma of a uniform surface exposure would be useful in estimating effective tolerance doses per volume of tissue irradiated.

SUMMARY

Anticoagulation measures, particularly citration, handicap phagocytosis in the presence of both normal and irradiated blood and plasma. Normal blood and plasma irradiated with 50 r and 100 r did not lose their increased phagocytosis enhancing properties after storing at 0° C. for forty-eight hours. Non-irradiated samples showed a slight increase in their phagocytic powers after storing. Heating for fifteen minutes at 65° C. did not destroy the opsonins and agglutinins brought out by small dose roentgen irradiation of blood and plasma. Softer rays seem to be more potent in producing such thermostable substances. Diluting the roentgen-ray dose optimal for phagocytosis does not cause a proportional decrease in the phagocytic power.

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DEPARTMENT OF TECHNIQUE

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A RADON MEASURING DEVICE

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INTRODUCTION

UP UNTIL a few years ago most radon seeds were measured by comparing them with a known amount of radium, using some type of string electrometer. Recently, a few devices using electronic components have been developed by Farmer,[2,3] Herbert,[4] Langmead,[6] Johns,[5] and others, for the measurement of small ionization currents produced by either roentgen rays or gamma rays. Many of these devices are rather complicated in nature, requiring batteries or specially regulated power supplies, and special electronic components. The authors have developed a radon measuring device using standard electronic components which may be operated from an unregulated power line. The device is easily operated and at maximum sensitivity gives a full scale reading on a microammeter for a radon seed of 1.5 mc. strength.

CIRCUIT

The basic principles of the device are illustrated in Figure 1. The current from a large ionization chamber is passed through a 10^{10} ohm Victoreen[8] grid resistor and the potential difference developed applied to the control grid of a 6J7 pentode (grid

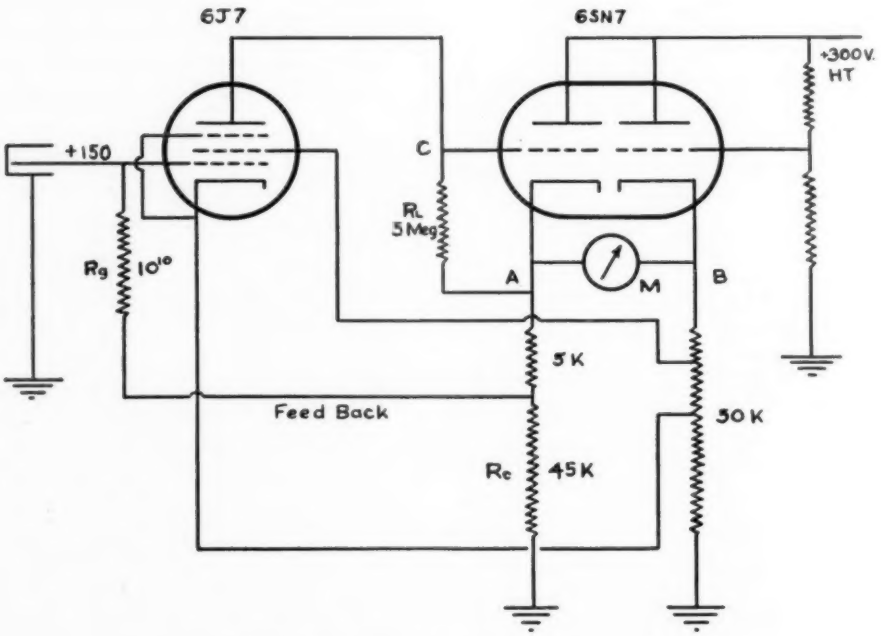

Fig. 1. Basic circuit diagram for the radon measuring device.

cap type). The grid current can be reduced to less than 10^{-12} amperes[1] by operating the heater at a reduced voltage of 4 volts, the screen grid at 10 volts and the plate at 20 volts. With this small grid current it is possible to keep the deflection due to grid current less than 1 per cent with a 10^{10} ohm grid resistor.

The output of the 6J7 is developed across R_L and applied between the grid and cathode of the first section of the 6SN7 (Fig. 1). It will be observed that the plate voltage for the 6J7 is obtained from the cathode of the 6SN7. This has a remarkable effect on the operation of the circuit for the voltage developed across R_L is applied *between* the grid and cathode of the cathode follower. If one considers the input voltage to the cathode follower as that developed across R_L the cathode follower now has a gain approximately equal to μ_2 where μ_2 is the amplification factor of the 6SN7. It can be shown that the voltage gain of the whole circuit (without the feed-back connection) is

$$\frac{-G_m r_1}{1+\left(\frac{r_1+R_L}{r_2+\mu_2 R_L}\right)\left(1+\frac{r_2}{R_C}\right)} \qquad (1)$$

where r_1 and r_2 refer to the plate resistances of the first and second tubes respectively, G_m the mutual conductance of the pentode and μ_2 the amplification factor of the second tube. For the components used in this circuit $r_2/R_C<1$ and $r_2<<\mu_2 R_L$ so that the gain is approximately given by

$$-\frac{G_m r_1 R_L \cdot \mu_2}{r_1+(\mu_2+1)R_L} \qquad (2)$$

If the plate of the 6J7 were connected in the conventional way the gain would be given approximately by

$$-G_m \frac{r_1 R_L}{(r_1+R_L)} \qquad (3)$$

When the plate resistance r_1 is very large compared with the load resistor, R_L expression (2) is about μ_2 times as great as (3). This is exactly the state of affairs encountered in this circuit with the 6J7 operating at reduced ratings. With a heater voltage of 4.0, screen 10 volts and plate 20 volts the mutual conductance is 7 micro mhos, and the plate resistance 200 megohms. The gain of the circuit using expression (2) is 420 while expression (3) yields a gain of 32. The gain of the circuit was measured and found to be over 400. Comparison of (2) and (3) indicates that the use of the cathode follower in this way can be considered as increasing the load resistance R_L by the factor μ_2. This produces a considerable increase in gain when the plate resistance is large compared with R_L but offers no increase when the plate resistance is small.

About 90 per cent of the output of the first half of the 6SN7 is fed back to the input of the 10^{10} ohm resistor so that the actual voltage gain is $(1/.9)(G/G+(1/.9))$ which for large values of the gain G (without feed-back) is independent of G and equals 1.1. The large gain of 400 inside the inverse feed-back loop serves to make the gain of the circuit independent of tube characteristics. It also keeps the 6J7 operating at almost exactly the same point on its characteristic curve regardless of the size of the input signal to *Rg*.

It should be noted that the cathode and screen of the 6J7 are connected to taps on the cathode of the second section of the cathode follower. This serves to keep the circuit balanced even with variations in the plate voltage of as much as ± 10 per cent. In the complete circuit of Figure 2 a second 6J7 is employed in a cathode control circuit, due to Miller,[7] to stabilize against changes in filament emission. This stabilization can be carried out simply by adjusting the 10,000 ohm rheostat in the cathode of the first 6J7 (Fig. 2) until the plate voltage of this tube is a minimum (Farley and Gove[1]). With this stabilization and a suitable ionization chamber connected, a line voltage variation of ± 5 per cent results in a zero shift of less than ± 1 per cent of the most sensitive scale. This is satisfactory for most conditions so

no stabilization is provided. Experience indicates that stabilization of the plate supply and no stabilization of the heaters results in poorer regulation with respect to line voltage variations. If line voltage variations are especially bad, a 25 watt second 6J7. This, by cathode follower action, alters the bias on the first 6J7. In lining up the circuit originally, it is necessary to alter the position of the negative feed-back point until the zero adjustment works properly.

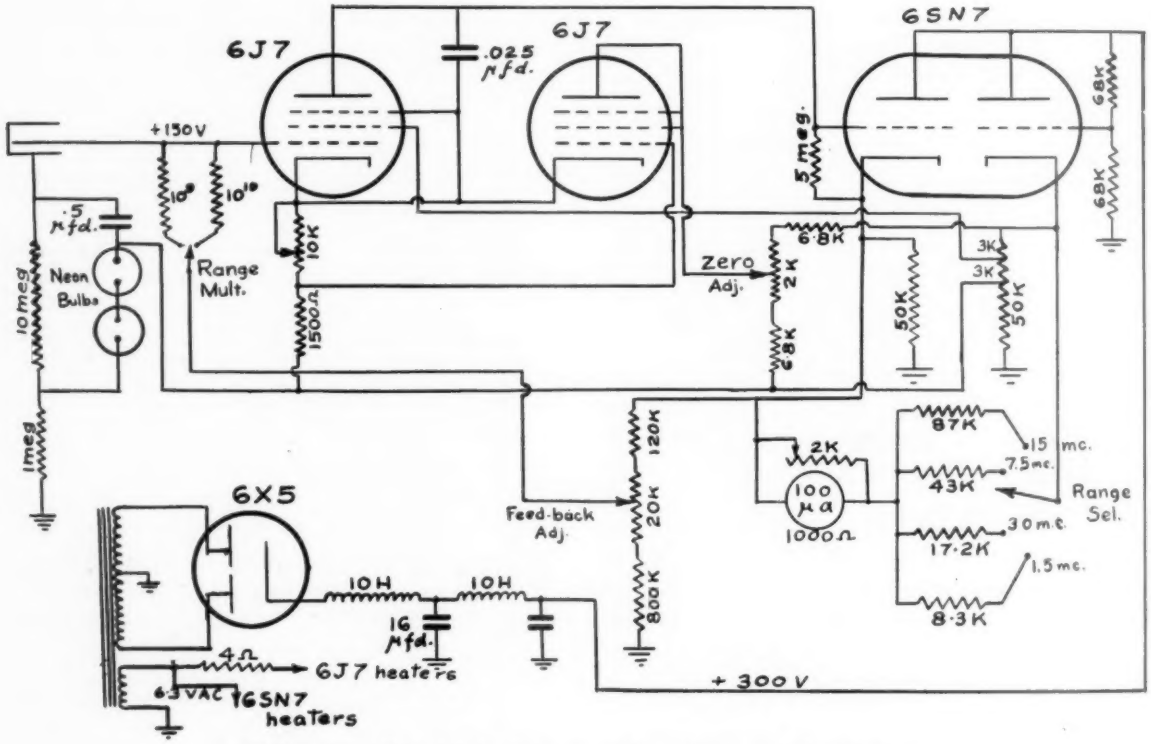

FIG. 2. Detailed circuit diagram of the radon measuring device.

constant voltage transformer will provide excellent stability.

The complete circuit diagram for the device is shown in Figure 2. The use of the second 6J7 as a triode for filament emission stabilization has already been described. The output is taken between the two cathodes of the twin triode. The sensitivity of the instrument may be changed in three ways. It may be altered by a factor of 10 by choosing either the 10^9 or 10^{10} ohm grid resistor in the input stage. It may be altered in steps by selecting the proper resistance in series with the microammeter, and small changes may be made by altering the resistance in parallel with this meter. The zero adjustment (Fig. 2) is conveniently made by altering the bias on the

IONIZATION CHAMBER

It was found convenient to build the ionization chamber in the same chassis as the electronic circuit. The radon or radium to be measured is dropped into a glass test tube which can be inserted into a brass tube which extends through the central part of the ion chamber. This chamber has dimensions 12 by 23 by 20 cm. The brass tube is covered with 0.020 in. of lead on the surface facing the air volume in the ionization chamber. It can be shown that the ionization current to be expected will vary as $\sqrt[3]{V}$ so that beyond a certain size it is not practical to increase the sensitivity by increasing the volume of the chamber. It was found that the lead lining increased the reading by about 20 per cent due to

photoelectric emission. Five sheets of copper are used for the ion chamber electrodes. These are placed 3 cm. apart. The two outer ones and the central one are connected together and to ground through 11 meg. (Fig. 2). The second and fourth electrodes are connected to the input circuit. Approximately 150 volts is applied between electrodes giving an electric field of 50 volts per cm. It is important to keep the capacity to ground small (50 $\mu\mu$f or less) because variations in plate supply are coupled to the 6J7 grid through the capacity of the ion chamber. Even with this small capacity it was found advisable to regulate the ion chamber voltage by means of two neon bulbs and to filter it against rapid variations in plate voltage (see Fig. 2).

CALIBRATION AND USE OF INSTRUMENT

The four range resistors are so chosen that full scale deflections are obtained with 1.5, 3.0, 7.5 and 15.0 millicuries when the 10^{10} ohm grid resistor is used. In actual practice, a standard amount of radium is placed in the holder, and the sensitivity adjusted slightly by varying the 2,000 ohm rheostat in parallel with the meter. Once this calibration has been carried out, no further adjustment is necessary and the instrument will read correctly on the other ranges.

To avoid stray radiation from the radium in the ionization chamber, the meter, the range selector and the zero adjustment were removed from the main chassis and connected to it by coaxial cables. A device was constructed which allowed one radon seed at a time to be dropped into the center of the ion chamber. After the measurement is made a small trap door is opened by remote control allowing the seed to drop through into a glass tube which carries it to a lead container. The instrument has been in use for some time for the routine measurement of radon seeds for the Saskatchewan Cancer Commission and proves to be dependable and easy to operate. Experience has shown that the apparatus maintains its calibration remarkably well and that actually the instrument rarely needs to be checked with a standard needle. Measurement can be made more quickly and with greater accuracy than with the string electrometer formerly in use.

Acknowledgments. The authors wish to acknowledge the technical assistance given them by Mr. J. R. Cunningham, radon technician, and to thank the National Cancer Institute and the Saskatchewan Branch of the Canadian Cancer Society for their financial assistance which made this work possible.

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EDITORIALS

RADIOLOGICAL UNITS

COMMENTS ON THE REPORT OF THE INTERNATIONAL COMMISSION ON RADIOLOGICAL UNITS, SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY*†

IN 1928 the roentgen was formally adopted as a unit of quantity of roentgen radiation. The definition was based essentially on the method of measurement involving the use of the open air standard ionization chamber. This method, however, was not suitable for the measurement of the gamma rays of radium or very high voltage roentgen rays. Therefore, in 1937 a more general definition of the roentgen was adopted, which specifically extended the use of the unit to (radium) gamma rays and to roentgen rays of equivalent photon energy.

Since that time the betatron and other devices have made possible the use of roentgen-ray voltages of an order of magnitude not envisaged in 1937. More important than this, however, has been the increasing medical use of internally administered radioactive isotopes in which beta radiation is solely or predominantly the agent responsible for the biological effects produced. Also, it must be borne in mind that other types of ionizing radiation (alpha rays, neutrons, protons, etc.) are being produced on a large scale. While the medical applications of these rays are very limited at present, the problem of measurement for biological dosage is important and acute, because it is essential for personnel protection. It is obvious, therefore, that a unit of quantity of radiation or dose, applicable to all types of ionizing radiation, is urgently needed.

It has been assumed since the beginning of modern roentgen-ray dosimetry that the energy absorbed by a cell or a tissue is responsible for the radiobiological changes produced therein. On this basis it would be expected that the simplest correlation between dose and effect would be obtained when the dose is expressed in terms of energy absorbed. The original definition of the roentgen was based on ionization in "free" air‡ because this made possible the practical measurement of a dose in terms of something that was closely related to energy absorbed in (soft) tissues. In the range of roentgen-ray wavelengths of therapeutic importance in those days (120 to 200 kv. roentgen rays), the absorption of energy by 1 gram of air and by 1 gram of soft tissue was not very different. It so happened also that in this limited range many biological effects did not show marked wavelength dependence,‖ and it was assumed by many that, other conditions being the same, a given dose in roentgens would produce the same biological effect, irrespective of the quality of radiation. This made the roentgen an eminently satisfactory unit from the point of view of the average radiologist.

However, when the wavelength range is greatly extended at both ends (much higher or much lower voltages) there is considerable difference in energy absorption by air and soft tissues.¶ Also, it is well

* Presented at the Fifty-first Annual Meeting, American Roentgen Ray Society, St. Louis, Mo., Sept. 26–29, 1950.

† Recommendations of the International Commission on Radiological Units (London, 1950). AM. J. ROENTGENOL. & RAD. THERAPY, Jan., 1951, *65*, 99–102.

‡ This expression was used extensively at that time to emphasize that the ionization to be measured was that resulting from the interaction of radiation and air only—excluding "wall effects," etc.

‖ Skin erythema was a conspicuous exception.

¶ What really counts is that the ratio of the two varies with the wavelength, not that the absolute values are different.

known now that the biological effectiveness of radiation depends on the ion density along the paths of the ionizing particles (the "specific ionization") when the dose is expressed in terms of energy absorbed by a cell or tissue. Therefore, a given dose of *roentgen rays expressed in roentgens or in terms of energy absorbed per gram of tissue* does not produce the same biological effect in a given cell or tissue, when the wavelength is varied sufficiently. Furthermore, the biological effectiveness of the radiation is apt to be different for every biological system and effect considered. This complicates the dosage problem, especially when all types of ionizing radiation are included. The complication is inherently of a biological character and cannot be removed by the choice of a unit based on any physical interaction of radiation and matter. Accordingly, whether the dose is expressed in roentgens (that is, energy absorbed in air) or in a unit based on energy absorbed in tissue, the biological effect cannot be expected to be the same when the specific ionization is very different.

It is evident from the foregoing that no physical unit* can fulfill the ideal requirement of making all biological effects of ionizing radiation appear independent of wavelength—or more generally, independent of specific ionization. If a biological effectiveness factor must be introduced, no matter how the unit is defined, it makes little difference in principle what physical basis is chosen. The problem then reduces to one of practicability and convenience in making dosage measurements.

The present definition of the roentgen explicitly limits its use to roentgen and gamma radiation. However, since the fundamental basis is ionization produced in air, and all ionizing radiations are capable of ionizing air, it would be possible to change the definition in such a way as to make the unit applicable to all ionizing radiations. This would necessitate drastic changes in the definition of the roentgen and the concepts it embodies. Careful consideration of the measurement problem, when all types of ionizing radiation are included, reveals that this is not a desirable solution. For instance, measurements of depth doses in terms of ionization in free air would necessitate the use of chambers with air equivalent walls of a thickness equal to the range of the most energetic secondary ionizing particles. This requirement introduces serious complications in the case of multimillion volt roentgen rays and especially in the case of neutrons.† In the latter case, an air wall chamber would give small readings with fast neutrons because of the absence of hydrogen and very high readings with slow neutrons because of the excessive amount of nitrogen as compared to tissue. Correlation of dose and biological effect would be a precarious problem indeed since, in a tissue irradiated with fast neutrons, there are always slow neutrons in varying proportions.

Similarly, the choice of any other basis for the definition of a unit applicable to all ionizing radiations would necessitate radical changes in the definition of the roentgen. Since the unit is now well established and radiologists are familiar with it, it is highly desirable to retain it for practical purposes in the roentgen-ray region in which no serious complications are encountered.

It is generally realized that, of the radiation traversing a tissue, only the part absorbed by the biological system can exert an influence on it. Therefore, we are all more or less accustomed to the concept of tissue dose in terms of energy absorbed per gram of tissue. Accordingly, a unit of dose for all ionizing radiations based on energy absorbed per gram of tissue does not require a reorientation of our way of thinking.

No serious difficulties arise in making dosage measurements in terms of this unit, with the accuracy required in radiobiological studies. The magnitude of the unit

* Actually in the present state of our knowledge no chemical or biological unit can fulfill the ideal requirement either.

† The construction of strictly air wall chambers in the case of neutrons would be a most difficult, if not impossible, task.

adopted by the Sixth International Congress of Radiology—1 erg per gram—makes comparison with the roentgen a little awkward. However, it should be remembered that the two units are not and cannot be related by a single proportionality factor throughout the range of roentgen-ray wavelengths available today and for all kinds of ionizing radiation. This is necessarily so because the difference in the atomic constituents of air and tissue brings about a difference in energy absorption, which can be small or great, depending on the kind and energy of the radiation under consideration. It is generally assumed that in the ordinary roentgen-ray region a soft tissue dose of 1 roentgen corresponds to an energy absorption of 93 ergs per gram of tissue. It would have been possible to adopt a unit with this magnitude (that is, 93 ergs per gram) and to give it a special name, such as, for instance, the "energy roentgen." Then in the roentgen-ray region of present interest to radiologists a tissue dose of 1 roentgen would be essentially equal to 1 "energy roentgen." However, the simplification would be more apparent than real since the equivalence is not constant and the radiologist would have to bear this in mind. Also, as already pointed out, when the specific ionization is quite different, one cannot expect to produce the same biological effect with a given dose of any radiation expressed in "energy roentgens." The field of activity of the radiologist is rapidly extending to the use of radioactive isotopes and types of radiation different from roentgen rays. The requirements of clinical radiation dosimetry are becoming more stringent. Therefore, the radiologist must be thoroughly familiar with the fundamentals of the dosage problem. In that case the magnitude of the dose unit and its name are completely irrelevant. There is only one respect in which a special name for the unit would be advantageous. Roentgen-ray dosage rate is generally expressed now in roentgens per minute. In terms of energy absorbed in tissue one would have to say "ergs per gram per minute," which is rather awkward. It might be mentioned in this connection that the matter of adopting a name for an energy unit has been left open by the International Commission on Radiological Units. It can be done at some future meeting if experience indicates its desirability.

It will be noted that in the definition of dose appearing in the first paragraph of the Commission's recommendations a definite meaning is given to the expression "energy absorbed." This was done to avoid ambiguity. With most types of ionizing radiation, energy is transferred from the radiation to the tissue by the intermediary of primary or secondary charged particles, which produce ionization, excitation, etc. This is the energy that is considered biologically effective, according to present thought. In some cases energy is taken up by nuclei and therefore absorbed from the radiation traversing the material, but what energy reappears in a form immediately available for ionization depends on the nuclear reaction involved. A striking example of this characteristic is the capture of a slow neutron (having practically no kinetic energy) by a nitrogen nucleus, followed immediately by the emission of a high energy proton which is strongly ionizing. In this case, practically no energy would be provided by the slow neutron "beam," and therefore the energy absorbed by the tissue *directly* would be very small, whereas that absorbed from the ejected protons would be considerable. This is the energy that must be considered in the determination of the dose. The situation is further complicated when radioactive isotopes are produced in the tissue by the radiation. In this case account must be taken of the dose delivered to the tissue by the isotopes even after the exposure to the primary radiation has stopped.

It will be seen from the foregoing that, as the field of medical radiology expands, the dosimetry problem becomes more complex. This is unavoidable. However, the radiologist may rest assured that the physicist will provide the necessary dosage

tables and charts for any new treatment conditions. In this connection it is interesting to note a significant new departure in the activities of the International Commission on Radiological Units. It has taken the initiative and assumed the responsibility of promoting the compilation and distribution of information relating to units and dosimetry. This is to be done on a continuous basis rather than at intervals coinciding with the International Congresses of Radiology as heretofore.

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GÖSTA FORSSELL
1876-1950

RADIOLOGY has lost one of its greatest leaders in the death of Gösta Forssell which occurred on November 13, 1950. It is a loss which will be felt, not only in his own country where he occupied a pre-eminent position, but throughout the entire medical world.

Forssell was born in Dalecarlia, Sweden, in 1876, and reached the beginning of his medical career at the turn of the century. He was one of a galaxy of pioneers, men of first class minds who laid the foundations of medical radiology. Among the men whom he especially mentions in his writings as his

teachers were those earliest pioneers in radiology, Albers-Schönberg of Hamburg, Holzknecht of Vienna, Rieder of Munich, and Béclère of Paris. Forssell was a peer among the leaders of those early days, and by frequent, friendly visits to the centers where they taught and by constant communication with those who were doing productive work both in Europe and America, he made himself completely familiar with all that was developing in radiology. He was thus able in the early years of the century to establish in Stockholm a radiological center, the influence of which has been world-wide.

Forssell's first radiological department was established in the Serafimer Hospital in 1906 and he remained its chief until his year of retirement, 1941. It was soon evident to him that the physical facilities at that institution could not then be expanded to provide the type of radiation therapy in cancer which he even then envisioned. He therefore founded in 1910 a small hospital which he called "Radiumhemmet," a name now famous wherever radiation therapy is known. It occupied rented quarters and had one roentgen therapy machine and 120 milligrams of radium. The story of Forssell's life as an administrator, a builder, and an organizer revolves around this institution. Its development into the magnificent clinical and research institution of the present day is a commentary on the courage, persistence, singleness of purpose, and far vision of Gösta Forssell. It was there as well as at the Serafimer that he gathered around him such outstanding contributors to radiological progress as Heyman, Berven, Åkerlund, Sievert and Lysholm. The combined work of these men, and of others who cannot be mentioned here, under the leadership of Forssell gradually built a great radiological clinic from the small beginnings of 1910. During the succeeding six years the support of the Anti-Cancer Association was augmented by grants in large amounts from the city of Stockholm and from private donations accumulated under the patronage of Her Majesty Queen Victoria, who became the institution's royal patron.

Radiumhemmet moved to new and larger quarters in 1916 with a greater number of beds, larger outpatient departments, and a research laboratory. In 1924 it was still further enlarged by the addition of well equipped research departments for radiopathology and radiophysics. In the year 1917 the State made substantial grants for purchase of radium and other purposes and from that time has provided free trans portation to and from their homes for cancer patients. The Clinic also received financial support from the Stockholm Medical School, the Caroline Institute, and additional gifts were received from time to time from individuals, including His Majesty King Gustaf V. In all of this is seen the guiding hand and inspiration of Forssell who was the Director of Radiumhemmet from its foundation until 1927 when he surrendered its direction to Elis Berven in order that he himself might assume the Chairmanship of the Anti-Cancer Association. In the year 1936 Radiumhemmet became officially attached to the Medical School, the Caroline Institute, as its teaching institution for radiotherapy. Forssell had been, since 1916, Professor of Medical Radiology and in 1936 Berven was called to occupy the chair of the newly created Professorship of Radiotherapy. Finally in 1937 came the consummation of Forssell's many years of organization in what is now called King Gustav V's Jubilee Clinic, so-called because the King dedicated to the project the nation's gift to him of more than five million crowns at the time of the celebration of the King's seventieth birthday in 1928. The King Gustav V's Jubilee Clinic was built as an integral part of the Caroline Hospital and comprises The Radiumhemmet, which the Anti-Cancer Association had turned over to the State, and Research Departments for radiophysics and radiopathology. Here, as a part of the University and its Hospital, Radiumhemmet continues its beneficent work for the people of Sweden, its fundamental re-

search in radiophysics and radiobiology, and its teaching of radiologists who will continue to assemble there from all parts of the world. It will stand through all the years to come as a monument to the great man who made it possible.

The direction and building of such an institution as Radiumhemmet would seem to constitute a life-work for any one individual, however great his powers. It was in fact only one of Forssell's many activities and was a means rather than an end in itself. One of the main interests of his life was the battle against cancer. For this purpose Radiumhemmet was organized, as well as the other Clinics at Lund, Upsala, and Gothenburg. Part of this story Forssell brought to us in his Caldwell Lecture delivered before the American Roentgen Ray Society in 1924 and published in this JOURNAL in October of that year.

It is rare to find in an individual who is a first-class administrator and organizer the ability to carry on original scientific research, but one of Forssell's greatest contributions was his investigation of the autoplastic muscular movements of the gastric mucosa. This occupied him for many years even after his official retirement. Various aspects of this research work were presented in publications in different journals from time to time. In 1922 he read a paper on the subject at the meeting of the American Roentgen Ray Society in Los Angeles. It was published in this JOURNAL in February, 1923.

Forssell's interests as a radiologist were by no means confined to the fields of research and radiotherapy. He maintained a continued interest and active participation in roentgen diagnosis from his earliest years. His papers on roentgen diagnostic subjects are characterized especially by correlation of the roentgen findings with physiology, pathology, and the clinical aspects of disease. He was at all times the great physician interested not only in medicine as a science, but he practiced it consummately as an art.

The "Bibliographie du Professeur Forssell—1899–1949," published in *Acta radiologica* (Vol. 32), comprises more than two hundred titles. It ranges over the entire field of radiology and in it one can follow the progress of roentgen diagnosis and radiotherapy for fifty years. In addition to this great literary output, Forssell was also the active Editor of one of the world's greatest radiological journals, *Acta radiologica*. He founded the *Acta* and was its Editor until his death.

The international contacts and influence of Forssell were truly world-wide. He was President of the Second International Congress of Radiology in Stockholm in 1938. There, under his guidance and largely the work of his hands, the rules and regulations which govern the International Congresses of Radiology, were adopted. His extraordinary abilities were never better exhibited than in the deliberations of the Executive Committee and the Assembly of an International Congress. His commanding presence, sound judgment, keen sense of relative values, his ability to marshal facts and present them in systematic sequence, and his fluent command of several languages, made him the natural leader in any international group. Men of many nationalities found it a privilege and honor to follow his leadership.

It is not for his contemporaries to attempt any final evaluation of the work and character of Gösta Forssell. That remains for the historian of future years, but we may be sure that he will forever occupy a large place in the history of Radiology. We who had the inestimable privilege of his acquaintance and the proud honor of his friendship can only record here words that betoken our respect and affection for one whose influence we shall feel as long as we live. It is recorded of him that he was a friend of his King. He himself was truly kingly in every aspect of his personality—noble in mien, kindly in all his dealings with his fellowmen, statesmanlike in his constructive work for humanity, a great physician and a noble man.

A. C. CHRISTIE, M.D.

MEMORIAL TRIBUTES TO GÖSTA FORSSELL

★

In Gösta Forssell there was blended the great radiologist and the original thinker. His vision and unerring judgment made him one of the first to see that radiation had given into the hands of the radiologist a potent weapon, not only for diagnosis but for the fight against cancer. He saw, too, that that weapon had to be forged and tempered in the furnace of inspired experimental use.

It must have been in the early years of this century that the idea first took shape in his mind of a special hospital for the exploration of that new agent, radium—and later roentgen rays—as a treatment for malignant disease. Such an idea could have but one outcome in a mind which recognised difficulties only to overcome them.

To few men can it have been given to realise a dream as fully as did Forssell, and his colleagues saw first the old and later the new Radiumhemmet develop into the world-famous hospital which has been the model for all who, like myself, have been entrusted with the organisation of radiotherapy services on a large scale. I therefore think of him first as an inspired leader in the field wherein my own work lies. But I know, too, how great were his contributions in other fields, especially as a talented teacher. This year it was one of my great disappointments that we did not have him with us at the Sixth International Congress of Radiology. He did so want to come and it would have been such a fitting conclusion to his lifelong associations with radiology.

Thinking back to previous Congresses, strangely enough my memories are not so much of what he said or did, but of sitting somewhere in the back of a Congress hall, rapt in sheer admiration for that magnificent head. It was a model worthy of an Epstein. It was a head which stood out in any gathering, so well did it symbolise the very man himself—great in character, granite in strength, yet with all of that mature beauty which reflects an inner integrity.

I quoted him in my opening address at the Sixth Congress, for no words could better express the aim and aspirations of our science, nor better revive memories of old friendship.

His spirit will be with us at Copenhagen and for many Congresses to come.

Ralston Paterson
President of the Sixth International Congress of Radiology
London, England

★

Professor Forssell was a much beloved friend for whom I had the greatest admiration. I met him for the first time in 1903 when he came to Paris to observe in the Services of the various hospitals the researches which were being carried on at that time. He had attended the Service of L. Brocq at the Hospital Broca where I performed my first experiments on the action of the roentgen rays on the skin and cutaneous lesions; he was greatly interested in my work and repeatedly mentioned later that he had commenced to practice radiation therapy as a result of my influence upon him. I confess that I consider it a great honor to have had a pupil of such outstanding quality as was Dr. Forssell.

He was a very charming man with very agreeable manners. He was a great scientist and an extraordinary inspirer of other people. The creative effort and the impetus which he has given to Radiumhemmet have made this institution a universally known center of research whence have come works of the highest value in the treatment of cancer.

The *Acta radiologica* which he has directed is one of the best journals of our specialty open to all interesting works and of irreproachable editing.

One of the great figures of the world of radiology has passed away but his work and memory will always survive in France where he had only friends.

J. Belot

Paris, France

★

In these times in which humanity, disconcerted and afraid, thinks with resignation of the present, and glimpses in the near future war and destruction, and when in this Occidental world the only aspiration is to save the natural rights of mankind, it is an occasion of consolation and hope to turn our eyes towards those intellectual and moral forces that so gallantly have succeeded in maintaining erect the banner of science and investigation, oblivious of their per-

sonal interests and their own lives in behalf of human nature.

Hereafter when we evoke the majestic image of Professor Gösta Forssell, at the peak of his seventy-five years, we bow with veneration before it, as we would toward the prototype of those exceptional moral and intellectual forces to which I have referred.

If we could find a numerous group of those scholars who because of their mental characteristics we call geniuses and due to their qualities of beauty and integrity of character are masters, there would be a different outlook for the future, if the destinies of the world were in their hands.

I have never been able to erase from my memory the solemn moment at the end of the banquet which adjourned the Fifth International Congress of Radiology, held in Chicago in 1937, when one of the members of the Indian Delegation humbly kneeled down before Professor Forssell to ask for his blessing. This blessing reached, through him, all the specialists in Radiology, and at the same time they in turn returned the blessing to the Master, praying to God that his precious life would be prolonged for many years so that he might continue to protect with his shadow the science of Radiology.

Gonzalo Esguerra-Gómez

Bogotá, Colombia

★

The extraordinary development of radiological science has been achieved by great men, marked out by destiny, from time to time.

Gösta Forssell was one of these who, at the moment when the radiology of the digestive tract was about to enter a period of greater precision, contributed his wonderful work on the roentgenological study of the gastrointestinal mucosa that marked a new era in the development of this specialty.

Pedro L. Fariñas

Habana, Cuba

★

Gösta Forssell has left us a monumental work, the result, during the last half century, of the enlightened and persevering labor of a man who gave up his whole life to the creation and development of our specialty. This work comprises the organization of medical radiology in an autonomous field and that of its teaching and training in every degree, the organization of the fight against cancer by radiations, as well as original, personal work, notably on the mucous membrane in the digestive tract.

Forssell was in every way a great animator. The impulsion which he gave to teaching made the Swedish school, which he created along with eminent collaborators and pupils, one of the most famous in the world. The organization of the struggle against cancer, which comprises the celebrated Radiumhemmet, owes him a great tribute. In the field of research, his first work—"Über die Beziehung des Röntgenbilder des menschlichen Magens zu seinem antomischen Bau; Beträge zur Anatomie und Physiologie des Magens"*—constituted a solid base of departure, opening a new road, rich not only in roentgen diagnosis but in general biology. His subsequent experimental research work led him to demonstrate that the mucous membrane is a contractile organ, and that the mucosal folds are not anatomically preformed; finally, with his collaborators he brought forth the theory of autoplasticity of the mucous membrane and described its mechanism, drawing attention to both the muscular and hydrodynamic factors. He gave birth, in this field, to innumerable publications in every country; all the monographs and original papers refer to his work.

An organ was needed for the diffusion of the ideas and the publications of this great school; the *Acta radiologica*, created by Forssell and collaborators in 1920, became this link. It is not necessary to recall the renown of this very excellent and international periodical. It contains, in the third and fourth numbers of 1950, a collection of papers from the Institute of Radiophysics of Stockholm dedicated to Professor Emeritus G. Forssell; this gives an idea of the repercussion of the Master's work. His part in the International Congresses of Radiology had no less importance; the one of 1928 in Stockholm, at which he presided, is still in all memories.

It was thus that Gösta Forssell gave, in this first half century, one of the finest contributions to the building up of medical radiology.

Besides the pioneer, there was the man. Happy father of a family, venerated by them, he was also an incomparable friend. Those who had the privilege of meeting him and remaining in contact with him, lose not only an affable,

* Published in 1913 in Supplementum 30 of the *Fortschritte auf dem Gebiete der Röntgenstrahlen*.

distinguished and cordial man, but a friend whose fidelity equaled his benignness and goodness.

René-J. Gilbert

Geneva, Switzerland

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In November, 1950, the flags waved at half mast in the hearts of the roentgenologists and radiologists of most countries of the cultured world when the sad news of the passing of one of the greatest pioneers of our specialty became known. Through the death of Professor Forssell the science of roentgenology has suffered in the true sense of the word an irreparable loss, since waningly small is the number of those who are in a position to produce so outstandingly at the same time in the diagnostic and therapeutic practices, in the various scientific domains, in research and teaching, in the fight against cancer, as well as in the organization of health insurance as a whole. His life work will have a permanent value.

Those who had the privilege to belong among his personal friends were also captivated by his extraordinary charm and noble personality so that the loving and tender memory of a friend will last forever.

G. Fedor Haenisch

Hamburg, Germany

★

Although not himself a gynecologist, Forssell has contributed much to radiotherapy in gynecology. In 1910–1913 he developed the so-called Stockholm method of radium treatment in cancer of the cervix uteri. The method which is empirically founded on observations of the effect of variations in the thickness of the filter used, the interval between treatments and the number of treatments may serve as an example of Forssell's masterly ability in clinical observation.

Already in its early years did Forssell realize that medical radiology would become a science of its own. He emphasized repeatedly that medical radiology to be of value should be centralized, diagnosis as well as treatment. It should be handled by well qualified medical men devoting their time and interest entirely to radiology and at institutions fully equipped to take care of the patients and the follow-up. Experience has shown that his ideas were right. He was an unusually far-sighted man and a great organizer.

Forssell's intelligence, his charm, and his great readiness to help made him beloved and admired by all who had the privilege of meeting him. His name will forever be associated with the history of medical radiology.

J. Heyman

Stockholm, Sweden

★

The passing of Gösta Forssell is deeply mourned by the German radiologists. Some of them have lost a very close friend. Forssell, who counted among his teachers the pioneers of German roentgenology and among them especially Albers-Schönberg, has in return throughout his life given much to the whole world and also to Germany through the fundamental investigations of diagnosis and therapy and through the excellent works of the Swedish radiological school created by him. The high standard to which Gösta Forssell raised radiology in his homeland and the important diagnostic and therapeutic institutions which he organized served as examples and pathfinders for the development in other countries. No one felt the necessity of a cooperation in radiology of the entire world as much as he has, and no one has surpassed him, always willing to help, in his endeavors to tie together again the threads of cooperation which have been broken by the storm of the times. In honoring his outstanding personality, to him go the unbounded thanks of his German friends.

H. Holthusen

Hamburg, Germany

★

The death of Dr. Gösta Forssell is a great loss, not only to Sweden, but to universal medicine, for his scientific contribution was very great, and there was still much more to be expected from his gifted intellect.

The Mexican radiologists express their grief by means of these lines, cordially united with their Swedish colleagues.

Manuel F. Madrazo

Mexico, D. F.

★

In Gösta Forssell we have lost another pioneer of radiology. Forssell was an illustrious figure in this comparatively new science. His scientific contribution and his research work

make one of the basic foundations on which this science has been able to build up its comprehensive and steadily increasing importance.

Gösta Forssell will always be remembered as one of the founders of medical radiology. His knowledge of the subject was universal. His talent for organization was unique and his ability to utilize it not only within the separate provinces of radiology but also in the international collaboration between radiologists throughout the world has been of outstanding and immeasurable significance.

We, his Scandinavian colleagues, may feel his loss more personally because we were bound to him with close ties of friendship, but Forssell's enduring contribution to the development of radiology has made him an international name which will always remain a glowing torch in the future.

P. Flemming Møller

Copenhagen, Denmark

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I deeply feel the honour to express in the name of the Società Italiana di Radiologia our regret and our sorrow for the loss of Professor Gösta Forssell.

In Italy Professor Gösta Forssell was very well known and loved, not only by those who had the privilege of knowing him personally, but by all the radiologists, who appreciated so much his rare qualities of scientist and gentleman. We have followed through his *Acta radiologica* the clever scientific activity of Sweden, activity that he represented in such a worthy way in all International Congresses of Radiology. His work and his memory will remain a precious guide for all of us.

Mario Ponzio
Secretary of the Società Italiana di Radiologia Medica

Torino, Italy

★

By the death of our dear colleague, Professor Gösta Forssell, the world has lost one of the greatest radiologists of our time.

Professor Forssell has almost certainly done more than anyone else to further the cause of the treatment of cancer by radiation. The Radium Clinics of Sweden, including the celebrated Radiumhemmet in Stockholm, owe their inception to him.

Forssell had a wonderful personality and inspired enthusiasm; his charm and humour will always remain in the memories of those who knew him intimately.

He was President of the Second International Congress of Radiology held in Stockholm in 1928, and all who had the privilege of attending will look back on that time with great pleasure.

I first met Forssell at the First International Congress, held in London in 1925, but had corresponded with him much earlier, as Secretary of the Röntgen Society. I also had the privilege of taking part, with him and Dr. Francis Carter Wood of New York, in the Round Table talk, broadcast from Chicago during the Fifth International Congress in 1937, when he told us of the part Sweden was playing in the fight against cancer.

All of us looked forward to meeting him again, last July, at the Sixth International Congress in London, but he was then very ill and unable to come. A letter was read from him, expressing his best wishes for its success. His presence was sorely missed by his many colleagues and friends.

Russell Reynolds

London, England

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We are faced with the sad news, which his friends have feared for more than a year: the news of Gösta Forssell's death. We all have proudly and justly called him our great master. We know how, thanks to him, radiology has developed in his country: a narrow field has evolved into a whole branch within our medical science. An enormous number of pupils bear witness to his scientific achievements. Radiumhemmet, which has been called the Mecca of Radiotherapeutics, is altogether his own work.

Whatever he began he led to amazing results. His theory of the autoplasticity of the mucous membrane has, to this day, not been fully exploited. His splendid appearance made him the dominating figure at all congresses, and his diplomatic gift enabled him to solve problems that seemed insoluble to the less privileged. But his highest qualities were his amiability and kindness of heart, by which he won the hearts of his colleagues, his pupils, and, above all, his patients.

Sweden has lost a great patriot, Europe a great European, and the world a great man. The radiologists of all nations lament the loss of a

personality whose memory they will forever cherish.

Hans R. Schinz

Zürich, Switzerland

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All British radiologists mourn the loss of a distinguished European colleague in the death of Professor Gösta Forssell. He was regarded by us in Great Britain as the doyen of diagnostic radiology in Europe. His personality, his academic distinctions, and his outstanding contributions to radiology, particularly the radiology of the gastrointestinal tract, are such as to make him perhaps the greatest figure in radiology of the past half century. British radiologists learned with the greatest regret of Professor Forssell's inability on account of illness to take his place of honour at the last International Congress of Radiology. British medicine paid tribute to him by the award of the Honorary Fellowships of the Faculty of Radiologists and of the Royal Society of Medicine. Radiology the world over is the poorer for his passing.

S. Cochrane Shanks

London, England

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Shoreham Hotel, Washington, D.C., Sept. 25–28, 1951.

American Radium Society
Secretary, Dr. J. E. Wirth, U. S. Marine Hospital, Baltimore, Md. Annual meeting: Hotel Claridge, Atlantic City, N. J., June 7–9, 1951.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y., Annual meeting: 1951, to be announced.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6.

Section on Radiology, American Medical Association
Secretary, Dr. P. C. Hodges, 950 E. 59th St., Chicago, Ill.

Alabama Radiological Society
Secretary, Dr. W. W. Anderson, Tuscaloosa, Ala. Meets time and place Alabama State Medical Association.

Arizona Association of Pathologists and Radiologists
Secretary, Dr. R. Lee Foster, 507 Professional Bldg., Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Atlanta Radiological Society
Secretary, Dr. T. F. Leigh, Emory Univ. Hospital, Emory University, Ga. Meets monthly, except during three summer months, on second Friday evening.

Brooklyn Roentgen Ray Society
Secretary, Dr. J. J. Daversa, 345 75th St., Brooklyn, N. Y. Meets monthly fourth Tuesday, Oct. through April.

Buffalo Radiological Society
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. F. A. Riebel, 15 West Goodale St., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, December, February, April, and June at Columbus Athletic Club, Columbus, Ohio.

Chicago Roentgen Society
Secretary, Dr. B. D. Braun, 6 N. Michigan Ave., Chicago 2, Ill. Meets second Thursday of each month, October to April inclusive at the University Club.

Cincinnati Radiological Society
Secretary, Dr. E. C. Elsey, 927 Carew Tower, Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. J. R. Hannan, 10515 Carnegie Ave., Cleveland 6, Ohio. Meetings at 6:45 P.M. on fourth Monday of each month from October to April.

Colorado Radiological Society
Secretary, Dr. Paul E. RePass, 306 Republic Bldg., Denver 2, Colo. Meets third Friday of each month at University of Colorado Medical Center or at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. E. W. Godfrey, 1676 Boulevard, West Hartford, Conn. Meets second Friday Oct. and April.

Dallas-Fort Worth Roentgen Study Club
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. J. C. Cook, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434-30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. T. H. Lipscomb, 30 W. Beaver St., Jacksonville, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. R. C. Pendergrass, Americus, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

Greater Miami Radiological Society
Secretary, Dr. David Kirsh, 712 duPont Bldg., Miami 32, Florida. Meets last Wednesday of each month at 8:00 P.M. at Veterans Administration Regional Office.

Houston X-ray Club
Secretary, Dr. Curtis H. Burge, 3020 San Jacinto St., Houston 4, Texas. Meets fourth Monday each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. William M. Loehr, 712 Hume-Mansur Bldg., Indianapolis 4. Meets second Sunday in May.

Iowa X-Ray Club
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society.

Kansas Radiological Society
Secretary, Dr. Anthony F. Rossitto, Wichita Hospital, Wichita, Kan. Meets annually with State Medical Society.

Kentucky Radiological Society
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Wybren Hiemstra, 1414 S. Hope St., Los Angeles 15, Calif. Meets second Wednesday each month at Los Angeles County Medical Assn. Building.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

* Secretaries of societies are requested to send timely information promptly to the Editor.

Maine Radiological Society
Secretary, Dr. C. F. Miller, Central Maine General Hospital, Lewiston, Maine.

Miami Valley Radiological Society
Secretary, Dr. G. A. Nicoll, 134 Apple St., Dayton, Ohio. Meets second Friday of fall and winter months.

Michigan Association of Roentgenologists
Secretary, Dr. R. D. McDuff, 220 Genesee Bank Bldg., Flint 3, Mich.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, Sept. to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. T. J. Pfeffer, 839 N. Marshall St., Milwaukee 2, Wis. Meets monthly on second Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. L. A. Nash, 572 Lowry Medical Arts Bldg., St. Paul 2, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Nebraska Radiological Society
Secretary, Dr. R. W. Blanchard, 1216 Medical Arts Bldg., Omaha, Nebr. Meets fourth Thursday of each month at 6 P.M. at Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. L. L. Robbins, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Harvard Club.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. J. L. Olpp, 49 Ivy Lane, Tenafly, N. J. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. J. E. Hemphill, 1420 E. Fifth St., Charlotte 4, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings by announcement.

Northern California Radiological Club
Secretary, Dr. C. W. Wauters, 701 High St., Auburn, Calif. Meets at dinner last Monday, every second month, except June, July and August.

Ohio State Radiological Society
Secretary, Dr. E. C. Elsey, 927 Carew Tower, Cincinnati 2, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. W. E. Brown, 21st & Xanthus, Tulsa 4, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. C. T. Jessell, 214 Medical-Dental Bldg., Portland 5, Oregon. Meets monthly 2nd Wednesday, 8:00 P.M.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport.

Philadelphia Roentgen Ray Society
Secretary, Dr. G. P. Keefer, American Oncologic Hospital, Philadelphia 4, Pa. Meets first Thursday each month October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary Dr. E. J. Euphrat, 3500 Fifth Ave., Pittsburgh 13, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Queens Roentgen Ray Society
Secretary, Dr. J. E. Goldstein, 88-29 163rd St., Jamaica 3, N. Y. Meets fourth Monday of each month except during the summer.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, Sept. to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Fred Zaff, 135 Whitney Ave., New Haven, Conn. Meets bimonthly on second Wednesday.

Radiological Section, District of Columbia Medical Society
Secretary, Dr. K. C. Corley, 1835 Eye St., N. W., Washington, D. C. Meets Medical Society Auditorium, third Thursday, Jan., March, May, Oct. at 8:00 P.M.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of New Jersey
Secretary, Dr. Peter Gianquinto, 685 High St., Newark, N. J. Meets annually at Atlantic City at time of State Medical Society and mid-winter at Elizabeth, N. J.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. A. V. Winchell, 40 Meigs St., Rochester, N. Y. Meets monthly on last Monday from September through May, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr.

St. Louis Society of Radiologists
Secretary, Dr. H. R. Senturia, Pasteur Medical Building, St. Louis, Mo. Meets fourth Wednesday each month, except June, July, August, and September.

San Diego Roentgen Society
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Tuesday at dinner.

Section on Radiology, California Medical Association
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. Harold L. Shinall, St. Joseph's Hospital, Bloomington, Ill.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Carolina X-Ray Society
Secretary, Dr. S. H. Fisher, 107 E. North St., Greenville, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas. Meets Galveston, Jan 19 and 20, 1951.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. R. C. Kiltz, 705 Medical-Dental Bldg., Everett, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

Wisconsin Radiological Society
Secretary, Dr. Irving I. Cowan, 425 E. Wisconsin Ave., Milwaukee 2, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco, 8, Calif. Meets Jan. to July, Lane Hall, Stanford Univ. Hospital; July to Dec. San Francisco Hospital.

Cuba, Mexico and Central America

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86 Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1.

Faculty of Radiologists
Honorary Secretary, Dr. J. F. Bromley, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Jean Bouchard, Suite 305, 1555 Summerhill Avenue, Montreal 26, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electrologie et de Radiologie Médicales
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

Australian and New Zealand Association of Radiologists
Honorary Secretary, Dr. Alan R.Colwell, 135 Macquarie St., Sydney, N.S.W.
Honorary Secretaries, State Branches:
New South Wales, Dr. E. W. Frecker, 135 Macquarie St., Sydney.
Victoria, Dr. T. L. Tyrer, 3 Lockerbie Court, East St. Kilda.
Queensland, Dr. J. Adam, 131 Wickham Terrace, Brisbane.
South Australia, Dr. R. de G. Burnard, 170 North Terrace, Adelaide.
Western Australia, Dr. A. M. Nelson, 179-B St. Georges Terrace, Perth.
New Zealand, Dr. E. G. Lynch, 12 Bolton St., Wellington.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mocsa, Avda. Gral Paz 151, Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central, Buenos Aires
Secretary, Dr. Oscar F. Noguera, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro, Sede, Cordoba
President, Prof. Dr. David L. Caro, Cerro 86, Cordoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo, Sede, Mendoza.
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Torres Focke, Av. 34, No. 17-34, Bogota, Colombia. Meets last Wednesday of each month.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Sociedad de Radiologica, Cancerologia y Fisica Medica del Uruguay
Secretary, Dr. Arias Bellini, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Allies, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10:30, X-Ray Dept., Akademia Gdansk.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

ALL-RUSSIAN ROENTGEN RAY ASSOCIATION, LENINGRAD. USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

SCANDINAVIAN ROENTGEN SOCIETIES
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

SOCIEDAD ESPANOLA DE RADIOLOGIA Y ELECTROLOGIA
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

SCHWEIZERISCHE RÖNTGEN-GESELLSCHAFT (SOCIÉTÉ SUISSE DE RADIOLOGIE)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

SOCIETA ITALIANA DI RADIOLOGIA MEDICA
Secretary Prof. Mario Ponzio, Ospedale Mauriziano. Torino, Italy. Meets biannually

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POSTGRADUATE COURSE IN ROENTGEN DIAGNOSIS OF DISEASES OF BONES AND JOINTS

A postgraduate course in roentgenographic interpretation of the diseases of bones and joints will be held at the Hospital for Joint Diseases, New York City, in affiliation with Columbia University, College of Physicians, from March 7, through May 23, 1951.

There will be a series of lectures covering the roentgenographic analysis of acute and chronic diseases of bones and joints including granulomas, neurotrophic lesions, neoplasms, and the manifestations of nutritional and metabolic bone changes in children and adults.

The course will consist of a didactic lecture lasting about one hour and followed by a lantern slide demonstration illustrating the disease or diseases under discussion. An average of approximately thirty-five to fifty lantern slides will be shown at each session, all representing material selected from cases seen at the Hospital for Joint Diseases during the past twenty-five years. Further information may be obtained from Miss Amelia Mater, Hospital for Joint Diseases, 1919 Madison Avenue, New York 35, New York.

THIRD ARGENTINE CONGRESS OF RADIOLOGY

The Third Argentine Congress of Radiology and First Panamerican Congress of Radiology will be held in Córdoba, Argentina, May 3–6, 1951. This meeting is organized by the Argentine Radiological Association.

Official themes will include the following: Abdominal tumors; mediastinal tumors; cancer of the lip; radiophysiopathology of the bronchial system; cancer of the eyelid; radiology of renal tuberculosis; and cancer of the larynx. The Barcia Conferences, under the direction of Dr. Carlos Osorio López, will be on the topic: "Present Status of the Early Diagnosis of Cancer of the Lung."

Dr. Lidio G. Mosca is honorary president of the Congress, Dr. Juan I. Zorrilla, president. Other officers and members of the Executive Committee include Dr. Raúl Mayer, 1st vice president; Dr. Victor Añaños, 2nd vice president; Dr. S. Di-Rienzo, secretary, Dr. Antonio Boher, Treasurer, and Doctors Juan A. Orfila, Manuel Quintana, Roberto Boher, Horacio Trejo, Néstor R. Montángero, Carlos A. Sánchez de Bustamente and Fernando Torres.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Jéquier, Michel. Dystrophie myotonique et hyperostose cranienne. (Dystrophia myotonica and cranial hyperostosis.) *Schweiz. med. Wchnschr.*, June 10, 1950, *80*, 593–599.

The author thinks that myotonic dystrophy (dystrophia myotonica) and cranial hyperostosis are the expressions at different stages of the same diencephalo-hypophyseal disorder of genetic origin. Thus he demonstrates cranial hyperostosis of varying degrees (predominantly frontal, temporo-occipital and basal) in 3 cases of myotonic dystrophy, in 1 suspicious case and in 2 healthy persons, all male members of one family (two generations). In another family, with the mother and daughter suffering from the disease, only the daughter shows cranial hyperostosis. In a sixth case of myotonic dystrophia, a man with no family history of the disease, again hyperostosis of skull is demonstrated. Fifteen cranial roentgenograms are presented. In the younger patients (17 to 39 years old) and in the non-familial case, the cranial anomalies were less pronounced and greatly resembled the images seen in the Morgagni-Morel syndrome. Hence the author surmises that there are different degrees in the development of hyperostosis.—*J. N. Sarian, M.D.*

Messimy, R., Berthet, G., and Cousin, R. Syndrome de Cushing à évolution prolongée avec volumineuse tumeur hypophysaire. (Cushing syndrome of prolonged course associated with a large hypophyseal tumor.) *Rev. neurol.*, April, 1950, *82*, 273–278.

A fifty-seven year old woman had the first manifestations of Cushing's disease at the age of twenty-nine, when amenorrhea and visual field changes developed. At the age of thirty-five there was abnormal growth of facial hair and masculine appearance of the facies was present. At the age of fifty-four, following a right hemiplegia with aphasia, the patient was hospitalized at which time diabetes and hypertension were discovered. At fifty-five another more severe right hemiplegia occurred.

Roentgen examination of the skull showed an extremely large sella turcica which was attributed to basophil adenoma, a diagnosis which was made on clinical grounds alone.—*Norman Simon, M.D.*

Sutton, David. The radiological assessment of the normal aqueduct and 4th ventricle. *Brit. J. Radiol.*, April, 1950, *23*, 208–218.

Examination can be made by air encephalography, air ventriculography, which is not so consistent nor successful, or by contrast ventriculography, which

is the most satisfactory method, as far as visualization of the structures is concerned. The problem is to find a satisfactory medium. Pantopaque has recently been used with success, and apparently no reactions have occurred.

A series of 100 normal encephalograms of children and adults was analyzed and a number of measurements made for comparison with published measurements of the posterior fossa.

(1) The distance between the dorsum sellae and the aqueduct varied between 2.9 and 4.1 cm.

(2) The distance from the dorsum sellae to the floor of the fourth ventricle varied between 3.1 and 4.1 cm. These two measurement ranges slightly expand the previously published figures.

(3) The length of the aqueduct was found to be 1.5 cm. which agrees with anatomists' figures.

(4) The width of the aqueduct was measured about 1 cm. below its upper and end varied between 1 and 2 mm.

(5) The height of the fourth ventricle varied between 1.3 and 2.1 cm. This was measured from the floor to the fastigium.

(6) The distance from the fastigium to the mouth of the aqueduct showed a wide range, the upper limit being 5.1 cm., but in several cases of pontine tumor, the figure was much larger.

(7) The angle between (a) a line joining the midpoint of the floor of the fourth ventricle to the mouth of the aqueduct and (b) another line joining the lowest points of the floor of the third ventricle was termed the ventricular angle. In all cases this varied between 85° and 95°. In 1 case presented, marked narrowing of this angle was the only abnormality seen in encephalograms of a patient who was later shown to have a glioma of the brain-stem.

There are two relationships which are usually more important than absolute measurements. One of these is the "Swedish line," which extends from the tip of the dorsum sellae through the lower part of the aqueduct to the skull vault. In a normal individual, the aqueduct lies either at or below the junction of the middle and lower thirds of this line. The second is "Twining's line," which extends from the tuberculum sellae to the internal occipital protuberance. The midpoint of this line always lies in or on the floor of the normal fourth ventricle. With these two relationships it is easy to determine any posterior displacement of the fourth ventricle. Of the two, Twining's line is more valuable.—*E. F. Lang, M.D.*

Ask-Upmark, E., and Ingvar, D. A follow-up examination of 138 cases of subarachnoid hemorrhage. *Acta med. Scandinav., 1950, 138,* 15–31.

Subarachnoid hemorrhages are less common than vascular lesions of the central nervous system parenchyma but are more common than subdural and epidermal hematoma. They are observed most frequently between the ages of thirty and sixty years. Although the majority occur after spontaneous rupture of an aneurysm, numerous instances are recorded following strenuous activity.

A hemorrhage within the subarachnoid space may generally be brought about by one of three underlying conditions: cerebral hemorrhage, arteriovenous aneurysm on the convexity of the hemisphere, and arterial aneurysm on the base of the brain. The present investigation deals with the last named. Dandy emphasized that basal aneurysms may be caused by embolic mycotic lesions in septic endocarditis, arteriosclerosis and congenital malformations.

In 47 postmortem examinations, 9 had renal malformations (in 5 cases, polycystic kidneys). Pulmonary edema was often seen.

The clinical symptomatology is briefly discussed. Sudden onset of meningitic symptoms and xanthochromic spinal fluid are outstanding. Migraine is not uncommon. Attention is called to the fact that the intracranial structures sensitive to pain are the basal arteries (Wolff, 1948).

Thirty-eight patients died during the initial attack, on the average at the ninth day. Early angiography and surgical intervention might save some of these patients. The 100 survivors were followed. Recurrences occurred in 39 cases (10 males with 4 fatalities, 29 females with 19 fatalities). Ten men and 3 women died from causes unrelated to the subarachnoid hemorrhage. At the time of follow-up examination there were still alive 33 males (6 of whom had had recurrent attacks) and 31 females (10 recurrences). Forty-one cases were traced for five years or less, 27 cases for five to ten years and 32 cases for more than ten years.

Without operation 1 out of 5 patients is expected to make a good recovery and to be able to take up his old occupation; 5 out of 5 remains crippled and 3 out of 5 die sooner or later from subarachnoid hemorrhage. The mortality in recurrent attacks is about twice as high as in the initial attacks. Cerebral angiography should be performed in appropriate cases as soon as possible.—*Charles Nice, M.D.*

de la Pena, A., and Anselem, A. Meningeal metastasis from a carcinoma of the prostate (its possible mechanism of production). *Urol. & Cutan. Rev.*, May, 1950, *54,* 262–266.

The authors report a patient, a male fifty years of age, with advanced carcinoma of the prostate who died as a result of an intracranial metastasis. The lumbar puncture revealed two cells in the cerebrospinal fluid.

The findings in this patient stimulated the authors to study a number of patients by injection of radiopaque media into the superficial and deep dorsal vein of the penis. By these studies they were able

to demonstrate a tendency for the periprostatic circulation to be directed toward the vertebral veins, as had been previously demonstrated by Batson in the cadaver. While the findings in these living patients were not conclusive, they tend to substantiate the views of Batson regarding the vertebral venous circulation.—*G. W. Chamberlin, M.D.*

Roach, John F. Cerebral angiography. *Am. J. M. Sc.*, May, 1950, *219*, 559–569.

The historical background leading up to the development of cerebral angiography is discussed. Dandy, in 1918, observed the striking changes in a patient with traumatic pneumocephalus, and proceeded to show the value of ventriculography and encephalography in neurological examination of the encephalon. This contributed immeasurably to the rapid progress made in neurosurgery since that time. In the early 1920's Egas Moniz of Lisbon began experimental work on injection of opaque material into cadavers and animals, and later on living humans. This method of study was quickly taken up by other European workers but it did not become a popular procedure in North America until relatively recently, that is in the 1940's.

Among the indications for cerebral angiography are the detection of lesions intimately associated with the blood vessels (such as aneurysm, arteriovenous fistula, thrombosis and angiomatous tumor), and the study of other pathological states, including almost all the tumors and non-neoplastic space-occupying masses. It should be used in patients in whom a vascular lesion is suspected and in all others in whom air studies fail to adequately demonstrate a supposed lesion. It is contraindicated in the acute state of a vascular accident and in advanced arteriosclerosis, extreme hypertension or cardiac decompensation. Also, in the case of any individual with a known sensitivity to a particular contrast medium, the use of such a medium is contraindicated but another contrast medium of different chemical family may be substituted.

Egas Moniz originally recommended the surgical exposure of the vessel to be injected, but this requires strict aseptic technique and special operative facilities. At the Johns Hopkins Hospital during the past two years the percutaneous route of injecting either the carotid or vertebral arteries without surgical exposure has been employed with highly gratifying success. In 268 attempts at carotid injections during 1948, 1949 and the first two months of 1950 there were only 24 failures—18 of these occurring in 1948, and 6 in 1949. Subcutaneous vertebral artery injection is a much more difficult procedure.

The contrast media in use today are of two types: organic iodine compounds and thorium dioxide solution. The latter has a greater radiopacity, it is less irritating than the organic iodine compounds locally and the general reactions are less pronounced than those occasionally seen with the iodine compounds. However, there is a definite hazard connected with its use, in that this radioactive material is deposited and retained in the liver, spleen and bone marrow for a long period of time. Its chief hazard is the possible carcinogenic effects of radioactive materials in general. The organic iodine compounds such as diodrast, neo-iopax and perabrodil, in 35 per cent solution (safer for rapid injection than more concentrated solution) are less opaque than thorotrast, are locally more irritating, and are much more apt to show general sensitivity reactions. In spite of this and because of the radioactive hazard of thorotrast, the author favors the use of organic iodine compounds for angiography.

At the Johns Hopkins Hospital there has been recently designed and built a double film transport mechanism which in conjunction with two roentgen-ray generators and two roentgen tubes permits the simultaneous making of films in two planes. With this equipment it is possible to complete the desired roentgenographic studies with only two injections of contrast material, or with only one if stereoscopic films are not required. A more efficient grid of the moving type is desirable because of the lower efficiency of a stationary grid of the Lysholm type, but this is not yet commercially available.

An accurate knowledge of neuro-anatomy is necessary for proper evaluation of cerebral angiograms. A forthcoming article by Curry and Culbreth discusses in great detail the normal vascular anatomy of the brain and its many variations.

The following changes must be studied carefully and evaluated in pathological alterations in the cerebrovascular system: (a) displacement; (b) abnormal caliber; (c) delay in filling; (d) delay in emptying; (e) abnormal arteriovenous communication; (f) abnormal distribution; (g) the formation of new vessels.

Lesions in the temporal lobe illustrate especially well the characteristic displacement of vessels by a space-occupying mass. In the lateral view, the middle cerebral vessels are displaced upward and frequently anteriorly, while the anterior cerebral is generally unaffected. In the anteroposterior projection the middle cerebral group is displaced medially.

Delay in emptying of vessels is frequently seen and is most important. When the normal vessels empty, opaque material is retained in the abnormal channels and casts a definite shadow on the subsequent film—the so-called "tumor stain." This sign is very beneficial in ascertaining the histopathological nature of a tumor (many tumors have a distinctly characteristic vascular pattern), as well as its physical size and location.—*S. G. Henderson, M.D.*

Pennybacker, J., Northfield, D. W. C., Parsons-Smith, G. P., and Tutton, G. K. Discussion on current trends in the management of the gliomata. *Proc. Roy. Soc. Med.*, May, 1950, *43*, 329–338.

Mr. Joe Pennybacker (The Nuffield Department of Surgery, Radcliffe Infirmary, Oxford): 716 cases of verified gliomas of the brain dealt with in the past 11 years are classified as follows:

Cerebellar astrocytoma	44	8.52%	16.5%
Ependymoma	17		
Medulloblastoma	57		
Spongioblastoma multiforme	282		39%
Astrocytoma (cerebral)	181		
Oligodendroglioma	44		44%
Unclassified	91		
Total	716		

In regard to cerebellar astrocytomas and ependymomas, complete removal followed by roentgen therapy is considered the proper procedure. In the series of medulloblastomas, the picture "was one of unmitigated gloom." The outlook in adult life is somewhat better. In children, surgical removal should be followed by radiotherapy in order to achieve the best results. In the group of spongioblastoma multiforme only 30 useful survivals (the longest 51 months) resulted. Surgery alone is considered powerless, and the combined efforts of the surgeon and radiotherapist are considered essential. The value and importance of histopathological verification is stressed. One case is reported in detail showing a dramatic and prolonged response to roentgen irradiation. Roentgen therapy alone is not considered sufficient but its proper role in conjunction with surgery is believed to be the most significant trend in the management of the gliomata.

Mr. D. W. C. Northfield: An increasing number of the gliomas are being treated with roentgen therapy and little else can be offered except some surgical palliative operation. The danger of destroying natural defense against a tumor by irradiation is pointed out.

Mr. G. K. Tutton: Preoperative assessment of the pathology of the tumor in gliomas is considered the most significant trend. Angiography is considered the most valuable means to this end. In 27 of 31 cases of glioblastoma a typical tumor pattern was seen. No surgery is suggested in cases of typical glioblastoma multiforme.—*C. N. Borman, M.D.*

Falconer, Murray A. Surgical treatment of spontaneous subarachnoid haemorrhage; preliminary report. *Brit. M. J.*, April 8, 1950, *1*, 809–813.

A leaking congenital aneurysm on the circle of Willis or adjacent arteries is the commonest cause of subarachnoid hemorrhage; less commonly it is due to leaking arteriovenous aneurysm or rupture of an atheromatous artery.

The condition is usually treated by rest and 50–60 per cent of the patients die and only 15–30 per cent make a satisfactory recovery. Bleeding frequently recurs, usually about the third week after the initial attack. Various surgical methods have been attempted, mainly internal carotid ligation; this usually carries a 20–30 per cent mortality rate in the presence of bleeding.

Falconer presents 40 cases, aged nine to sixty-seven, treated surgically with a 12.5 per cent mortality rate and 65 per cent full recovery; most of these cases were those which had developed recurrent bleeding while still in the hospital. Surgical investigation is started within a few days of bleeding.

He routinely does carotid arteriograms and exposes both the common carotids and injects contrast material under local anesthesia. The 31 aneurysms demonstrated in 30 patients were situated as follows: 14 on intracranial internal carotid, 5 at bifurcation of internal carotid, 3 on the middle cerebral and 9 on the anterior cerebral artery. In addition there were 3 cases of leaking arteriovenous malformation, one leak in the circle of Willis without aneurysm formation and 6 cases in which the bleeding point was not discovered by carotid arteriography.

The treatment method of choice is stage ligation of the common carotid and later ligation of the internal carotid since the former procedure may not be sufficient for permanent relief. In some aneurysms, particularly those on the circle or its distal branches, there may be establishment of collateral circulation, and whenever possible, direct intracranial approach to the aneurysm is made and it is "trapped" or wrapped with muscle.

Falconer regards subarachnoid hemorrhage as a surgical emergency demanding immediate carotid arteriography and surgical treatment.—*Martha E. Mottram, M.D.*

Carroll, Wynton H. Roentgen manifestations of acute and healed toxoplasmic encephalomyelitis. *Radiology*, April, 1950, *54*, 554–558.

The clinical and roentgenographic findings of 2 cases of infantile toxoplasmic encephalomyelitis are presented.

One case of the acute form in an infant presented initial symptoms of convulsions at the age of two weeks. Pneumoencephalograms revealed symmetrical dilatation of the entire ventricular system. There was no evidence of intracranial calcification. Toxoplasma organisms were found at autopsy.

The second case, a five year old male, presented findings of the healed disease. There was microcephaly, lateral mystagmus of the right eye with opacity of the right vitreous and chorioretinitis on the left. Roentgenographic examination of the skull revealed numerous areas of calcification scattered

throughout both cerebral hemispheres. Pneumoencephalogram was normal. Neutralization antibody and complement-fixation tests for toxoplasma were not done.

The contrasting features of adult and infantile toxoplasmosis are described.—*A. W. Sommer, M.D.*

Lewin, J. R., Wycis, Henry T., and Young, B. R. Roentgen diagnosis of herniation of the brain into the spinal canal (Arnold-Chiari deformity) by pantopaque myelography; report of a case diagnosed preoperatively. *Radiology*, April, 1950, *54*, 591–594.

A case of herniation of the brain into the spinal canal diagnosed preoperatively by pantopaque myelography is reported. There was almost complete block of the pantopaque at the skull produced by a lesion with a peculiar lobulated inferior border with a central incisura.

A diagnosis of Arnold-Chiari deformity was feasible in this case without cervical myelography because of multiple bony developmental deformities, but when these associated abnormalities are not present, cervical myelography is of definite value in making a differential diagnosis.—*E. E. Seedorf, M.D.*

Wigh, Russell. Mucoceles of the frontoethmoidal sinuses; analysis of roentgen criteria; relation of frontal bone mucoceles to ethmoidal sinuses. *Radiology*, April, 1950, *54*, 579–590.

Mucoceles of the nasal accessory sinuses are rare, benign mucous-filled cysts, which may fill a sinus and expand to cause contiguous bone destruction. Retention cysts have the same type of wall and usually a serous fluid content but do not, as a rule, completely fill the chamber of a sinus. There is actually a great similarity between retention cysts and mucoceles with the main difference being the clinical and roentgenological evidence of pressure and expansive bone erosion in the case of mucoceles. Mucoceles are very rare anywhere except in the frontal sinus region while retention cysts are most common in the antra.

The usual clinical finding in expanding mucocele is displacement of the eye downward, forward, or laterally. Secondary visual changes take place as the mucocele enlarges. In spite of the fact that the sinus is filled with a fluid-containing cyst, the mucocele is usually radiolucent because the surrounding sinus wall has been destroyed and therefore good contrast does not exist.

Normally the frontal sinuses have a scalloped border and this always disappears as the result of mucocele pressure. A frontal sinus containing a mucocele is larger than the opposite sinus but in a few of the cases reported the mucocele did not fill the sinus. Opaque medium injections will help differentiate such a condition. Ethmoid cells closely related to the frontal sinuses may be the origin of a mucocele which gives atypical signs such as lateral displacement of the eye with a bulge in the nasofrontal angle. Ethmoid cells extending into the frontal region may give rise to a mucocele which has the clinical signs of a frontal sinus mucocele.

In differential diagnosis, malignant tumors destroy the sinus outline in an irregular and invasive manner while in an inflammatory process the sinus outline is not altered but when bone changes do occur they are very irregular.—*C. A. Stevenson, M.D.*

Baclesse, F., and Letouze, G. Considérations radio-cliniques à propos de 14 cas d'adamantinomes. (Clinico-radiologic considerations in 14 cases of adamantinoma.) *Presse méd.*, April 5, 1950, *58*, 372–374.

Adamantinoma is not a frequent tumor. At the Curie Foundation over a thirty year period, 14 cases were encountered, of which 10 were treated. The ages of the patients in this series varied from thirteen to sixty-nine years with the majority occurring between twenty and sixty years. These lesions are much more frequent in the mandible (12 cases) than in the maxilla (2 cases). The most frequent site of development was in the region of the angle of the mandible from where they extended toward the ramus and the body.

Roentgenologically there are three classical varieties of this tumor: (1) Areolar type, with a pronounced "honeycomb" aspect, very infrequent; (2) multilocular type, most frequent of all, giving an appearance which resembles, "gruyère cheese" or "soap bubbles"; and (3) unilocular type, less frequent than the latter.

Differential diagnosis lies primarily between giant-cell tumors, metastatic tumors from glandular epitheliomas (viz., thyroid), and mixed tumors of the salivary gland (occasionally a mixed tumor of the parotid may extend into the maxilla creating an osteolytic cystic appearance which may be incorrectly interpreted as due to a primary tumor of the maxilla). The adamantinomas grow very slowly, and produce lymphatic or visceral metastases only in rare instances. Local malignity is their chief characteristic.

Treatment should be complete surgical excision beyond the lesion and extending into healthy bone. Recurrence is frequent and is the chief reason why radiation therapy may be tried. The authors have obtained satisfactory results with roentgen rays used in high doses, administered through small fields, and fractionated (of the order of two to two and one-half months). The authors feel that this treatment stabilizes the development of the tumor and prepares the way for more successful surgery. —*W. M. Loehr, M.D.*

Neck and Chest

Boucot, Katharine R., and Cooper, David A. A critical evaluation of mass roentgen surveys. *J.A.M.A.*, April 22, 1950, *142*, 1255–1258.

In this article the authors evaluate the results of mass roentgen surveys for the detection of tuberculosis in Philadelphia. It is pointed out that the goal is not accurate diagnosis, on the basis of the photofluorograms alone, but rather the screening out of significant or potentially significant pulmonary disease. The chief value of the mass surveys has been the detection of tuberculosis and pulmonary neoplasms. Any persistent pulmonary infiltration not definitely diagnosed as tuberculous should be considered potentially malignant for the same reason that it is wise to consider all pleural effusions tuberculous until proved otherwise.

It is noted that it is important to consider the population segment to be studied. Primary school children surveyed in 1946 showed that only 0.3 per cent were possibly tuberculous, and none of these have been found to have active tuberculosis up to the time of writing this article. On the other hand, 8.4 per cent of diabetic patients surveyed in 1946 showed possible tuberculosis. Other groups fell in between these extremes, such as food handlers, industrial workers, and the routine admissions and outpatients of the Philadelphia General Hospital. In answer to questions by discussants of this paper, it was stated that a follow-up on 500 significant cases showed 0.6 per cent clinically active cases of tuberculosis.

It is stated that the photofluorograms should be over-read rather than under-read. It is also contended that the survey physician should be the responsible person to initiate measures leading to an adequate follow-up on suspected cases.—*D. S. Kellogg, M.D.*

Yerushalmy, J., Harkness, J. T., Cope, J. H., and Kennedy, B. R. The role of dual reading in mass radiography. *Am. Rev. Tuberc.*, April, 1950, *61*, 443–464.

The errors in interpretation of chest films in mass roentgenography are of two types: (1) false positive readings (evidence of inflammatory disease requiring clinical follow-up), and (2) false negative readings. One method used in an attempt to lessen errors of interpretation is dual reading. This means that a series of films is read by identification numbers and later the entire series is again read in the same way by the same or another reader without knowledge of the first readings.

Dual reading diminishes the number of false negatives and increases the number of false positives. In evaluating the usefulness of the method the number of false positives and the time and trouble these cause the patient and physicians must be balanced against the number of additional truly positive diagnoses made.

A set of 1,800 photofluorograms taken on unselected university students was subjected to ten independent interpretations by six radiologists. As a result of the ten independent interpretations, 254 photofluorograms were called positive on one or more readings. These 254 students were recalled for 14 by 17 inch films, and these films were interpreted independently six times. Films unanimously interpreted as negative were considered negative and those unanimously considered positive form the group of 30 "truly positive" cases. Seventeen cases on which opinion was divided were arbitrarily excluded from this study, and also excluded were 9 cases of non-tuberculous chest disease. The results were compared, not only to determine the number of additional truly positive and false positive cases recognized, but also to determine a modification of the method which would afford the maximum accuracy. By subjecting all of the films with contradictory diagnoses to a single reviewer, or a panel of three for review, the number of false positives was materially reduced, and the greater proportion of the truly positives retained. A single competent reviewer achieved as good results as the panel of three.

It is of particular interest that the average reader missed 32.2 per cent of truly positive diagnoses and gave false positive diagnoses on 1.7 percent of the truly negative films. By dual reading the average number of additional truly positives recognized was 18 per cent of the total.—*Lois Cowan Collins, M.D.*

Lester, Charles W. Funnel chest and allied deformities of the thoracic cage. *J. Thoracic Surg.*, April, 1950, *19*, 507–522.

Funnel chest deformity is produced by a short central tendon of the diaphragm. When the muscle contracts during inspiration the lower end of the sternum is drawn backward. The character of the deformity depends on which portion of the central tendon is shortest—a symmetrical funnel being due to shortening of the midportion of the central tendon, while short lateral leaflets will produce a transverse groove across the anterior chest wall below the xiphoid. Various combinations are possible. Secondary deformities are increased kyphosis of the thoracic spine and increased downward slant of the ribs. This gives a characteristic appearance on the roentgenogram. The heart is most affected by the deformity. It is displaced to the left and compressed, which causes cardiac embarrassment. This is enhanced by decreased respiratory capacity and frequent respiratory infections.

Indications for surgery are greatly limited activity and defective physical development as well as psychologic considerations. Surgery should be done as early as possible. After five years of age, permanent

changes in the bony structures have developed which cannot be entirely corrected. However, surgery will always bring about relief of pressure symptoms.

The various surgical techniques are described.—*F. M. Reis, M.D.*

Dailey, M. E., and Lindsay, S. Thyroid neoplasms in youth. *J. Pediat.*, April, 1950, *36*, 460–465.

The authors encountered 4 benign and 19 malignant tumors of the thyroid in patients under twenty years of age at the University of California Hospital. The pertinent historical data and physical findings of these 23 cases are summarized. All the benign tumors and all but 4 of the malignant tumors were in female patients. Thirteen of the malignant cases had metastases.

Pressure symptoms included dysphagia, cough, dyspnea, choking, and hoarseness. Hoarseness associated with vocal cord paralysis was an ominous finding. The most important physical finding was the discovery of a nodular goiter. In the author's series 59 per cent of all non-toxic nodular goiters in patients under twenty years of age were malignant. This fact emphasizes the importance and seriousness of nodular goiter in the young.

Eleven of the present series were papillary adenocarcinomas. Subtotal thyroidectomy is indicated in all nodular goiters in individuals under twenty years of age. If malignancy is evident radical thyroidectomy is carried out with removal of all involved nodes and often a radical neck dissection will be necessary. Radiation therapy is used for inoperable cases only. Aggressive attack is warranted even in the presence of local and visceral metastases in view of long range survivals. Experimental therapy with radioactive iodine was used in only 3 cases which showed sufficient uptake with test doses to warrant such therapy. This is never more than an adjunct to adequate surgery.—*R. M. Harvey, M.D.*

Di Rienzo, S. Bronchial dynamism. *Radiology*, Aug., 1949, *53*, 168–186.

The bronchi are not simply "air passages" or air conduits. They possess anatomic and physiologic characteristics destined to fulfill a much more important function than that of mere air-distributing channels.

The bronchi were studied with the aid of iodized oil by fluoroscopic observation and films during inspiration, expiration and while the patient coughed. Studies were also made of bronchi to demonstrate the changes occurring in asthma and bronchiectasis.

The caliber of the bronchus is increased during inspiration and reduced during expiration. In asthma slight defects in the wall of a bronchus are noted giving the appearance of sphincters preventing the normal ventilation of the lungs.

In the act of coughing waves are noted simulating peristalsis that aid in the removal of material from the bronchus. These waves start in the small bronchi and extend to the trachea.

It is also shown that in bronchiectasis the secretions are not expelled by coughing. The lack of peristalsis results from injury to the mucosa and muscular lining of the bronchus. These dynamic characteristics make possible a differentiation between surgical and non-surgical bronchiectasis.

The article is well illustrated and should be studied by persons interested in the dynamics of the bronchial lining.—*V. L. Peterson, M.D.*

Baranger, A., Delie, P., and Lemoine, J.-M. Évolution de la bronchographie. (Advance in bronchography.) *Presse méd.*, April 5, 1950, *58*, 365–367.

One of the main difficulties accompanying the use of regular lipiodol in bronchography is the stagnation of the lipiodol in the bronchial divisions and persistence of this material in the alveoli and pulmonary parenchyma for weeks and months after bronchography. This slow absorption and persistence of lipiodol within the lung prevents successful bronchoscopy, prevents the repetition of bronchographic studies when results are unsatisfactory on the first attempt, and always interferes to varying degree with the interpretation of subsequent chest films.

The advance in bronchography described in this paper consists in the announcement of a new contrast medium for this procedure. It is a di-iodinated molecule which is hydrosoluble and sufficiently viscous. It is rapidly eliminated by the urine. Within two hours following the bronchial injection of the new substance the lung fields are cleared. The bronchography may be repeated if necessary, and the patient studied with subsequent films without there being residual contrast medium in the lung fields. Several such substances are under study by French pharmaceutical houses. One of them is at present produced by the Swiss firm of Cilag and called "Ioduron B."

One important technical point—the tracheobronchial anesthesia must be increased and more potent for the newer rapidly absorbed hydrosoluble iodinated substances than for regular lipiodol.—*W. M. Loehr, M.D.*

Byrnes, Colman K. Post-cricoid cancer. *Irish J. M. Sc.*, May, 1950, *6*, 236–243.

Cancer developing in the segment of the esophagus between the level of the opening of the larynx and the thoracic inlet is difficult to diagnose and more difficult to treat.

Dysphagia is a late symptom of post-cricoid cancer, yet most of the patients with this disease do not usually present themselves to their physician until dysphagia is present. The author indicates that

Plummer-Vinson syndrome may be a precursor of post-cricoid cancer. This syndrome quickly clears up on iron therapy, but such patients should be frequently re-examined and by so doing cancer in this region may be recognized in its early stage.

Surgery, if possible, is the choice method of treatment. Roentgen therapy is used when glandular metastases are present, or in the more undifferentiated type of lesion. Despite opinion to the contrary, the author believes that a combination of roentgen therapy and surgery may help. A preoperative course of roentgen therapy is being given in a number of patients.—*W. M. Roy, M.D.*

Clerf, Louis H., Shallow, Thomas A., Putney, F. Johnson, and Fry, Kenneth E. Esophageal hiatal hernia. *J. A. M. A.*, May 13, 1950, *143*, 169–172.

The authors report an analysis of 110 cases of esophageal hiatal hernia seen at the Jefferson Hospital, Philadelphia, during a fifteen year period, 1934 through 1949.

Age range was from twenty-nine to seventy-eight, but only 7 patients were under forty, 78 being between fifty and seventy. Duration of symptoms was over one year in more than three-fourths of the cases with a range of less than three months to over twenty years.

Dysphagia and pain were the chief symptoms, the pain being either precordial or epigastric in most cases. In early cases, pain was mild and infrequent, becoming more constant and more severe as the condition progressed.

Both roentgenography and esophagoscopy were employed in diagnosis in all cases. Thirteen, diagnosed esophagoscopically, were incorrectly diagnosed roentgenographically, being considered as normal, or having achalasia, carcinoma, or esophageal diverticulum. Examination in the recumbent position is stressed as an essential part of the roentgenographic routine. In determining the presence of ulceration, esophagoscopy was clearly superior, ulcers being demonstrated in 39 patients by esophagoscopy, but in only 5 by roentgenography. This discrepancy is explained by the fact that ulcerations were usually superficial and covered by exudate.

Excluding patients with multiple lesions, 35 of the group had had previous errors in diagnosis with carcinoma, achalasia, duodenal ulcer, and coronary thrombosis as the commonest.

Sixty-nine per cent of the patients were treated by medical and mechanical measures. The former comprised bland, low-residue diet, swallowed in small amounts, semirecumbent position for sleeping, antispasmodic drugs and alkalis. Mechanical treatment consisted of relief of obstruction by dilatation and topical application of 10 per cent silver nitrate to the ulcers.

Surgical treatment was considered indicated in patients under fifty-five years of age whose symptoms were progressive or whose hernias increased in size. The presence of one-third of the stomach above the diaphragm, severe and recurrent hemorrhage, and/or incarceration were other indications for surgical treatment. Operative procedures were advised in 31 per cent of the cases but were submitted to by the patients in only half this number. Of the surgical group, half had repair of the defect, the other half phrenic exeresis. Results in this group are not reported.—*L. K. Sycamore, M.D.*

Canónico, Abel N., and Eguía, Osvaldo. La propagación esofágica del cáncer gástrico; su importancia clinicoquirúrgica. (Esophageal extension of gastric cancer; its clinical surgical importance.) *Prensa méd. argent.*, May 26, 1950, *37*, 1112–1118.

With the advent of radical surgery in cancer of the stomach, the esophageal extension of this lesion, especially when located in the cardia, fundus or upper half of the stomach, has acquired considerable significance. The extension may occur (1) through the intramural lymphatic net-work or (2) by direct continuity.

(1) The lymphatics of the gastric mucosa, primary site of the cancer, originate immediately underneath the epithelium. They then pass through the muscularis mucosae into the large lymphatic sinuses of the submucosa and from there through the muscular layers of the stomach into the lymphatic plexus of the subserosa. There is widespread connection of the submucous and subserous lymphatic spaces of the stomach with those of the esophagus permitting an ascending intramural passage of the neoplastic cells. This passage may assume two forms: (a) continuous lymphatic permeation which clinically may lead either to a solid mass comprising the primary lesion and metastatic extension or to two separate masses, the lower constituting the primary lesion of the stomach and the upper the esophageal extension, and (b) embolic spread to various points of the lymphatic network, usually producing the same clinical appearance as described in (a). Regardless of the mode of extension, the submucous lymphatics appear to be involved most frequently giving rise to small tumors which elevate the esophageal epithelium without ulceration.

(2) The esophageal extension by direct continuity may occur along the submucosa, muscularis, subserosa or all layers of the stomach. Clinically, it may manifest itself as linitis plastica or as forms of adenocarcinoma. One may accept the view that rapidly growing cancers extend principally by lymphatic emboli, whereas the slowly growing cancers invade by continuous lymphatic permeation.

The authors studied the autopsy material in 14 cases of carcinoma of the upper part of the stomach,

including linitis plastica, to determine if any esophageal extension has taken place. It was noted that in 9 of the 14 cases the cancer of the stomach produced definite intramural invasion of the esophagus. Metastatic tumors were found at distances of 2 to 12 cm. from the cardia. Photographs of the specimens, photomicrographs and sketches of the primary carcinoma of the stomach and its respective esophageal extension are presented in 6 cases.

This observation constitutes an anatomopathologic finding of considerable interest but is even more important from the standpoint of surgical treatment. In performing radical resection of the carcinoma it explains (1) why the esophageal end of the specimen on histopathologic study often contains cancer cells indicating a wider extension than was suspected at operation, and (2) why a recurrence at the site of anastomosis or its vicinity is so frequently seen.

A review of the literature shows that the esophageal extension of the gastric carcinoma is reflected in several of the surgical statistics. Pack and McNeer recently reported that in 40 per cent of the resections performed for malignant tumors of the cardia, fundus and upper half of the stomach the esophagus was definitely involved by extension of the tumor. Sherman, in examining a series of 25 cases of tumors of the upper portion of the stomach roentgenologically, was able to demonstrate esophageal extension in 19 cases.

The conclusion is reached that systematic roentgenologic and esophagoscopic studies of the lower esophagus are indispensable in all tumors of the upper third of the stomach. At operation, external palpation of the esophagus is not sufficient to rule out the presence of intramural esophageal extension of the tumor, but a histopathologic study by frozen section of the upper end of the resected specimen is necessary before the anastomosis is effected.—*T. Leucutia, M.D.*

Shek, J. L., Prietto, C. A., Tuttle, W. M., and O'Brien, E. J. An experimental study of the blood supply of the esophagus and its relation to esophageal resection and anastomoses. *J. Thoracic Surg.*, April, 1950, *19*, 523–533.

This series of experiments was done to ascertain whether or not the blood supply of the esophagus of the dog is adequate to tolerate a resection with end-to-end anastomosis. Arteriographic studies of the esophageal blood supply and the actual healing in the experimental animal revealed the fact that apparently the blood supply is much more adequate than had previously been supposed. The entire thoracic esophagus can be freed of its thoracic blood supply, resected and anastomosis made with good healing. Apparently the blood supply from the gastric arteries is sufficient to nourish the entire esophagus Even the right gastric artery alone is sufficient to keep the esophagus viable and heal an anastomosis. In the discussion of this paper doubt was expressed that the findings could be applied to the human esophagus.—*F. M. Reis, M.D.*

Donnelly, Brian. Congenital oesophageal atresia with tracheo-oesophageal fistula; report of five cases and a plea for early diagnosis. *Lancet*, April 8, 1950, *1*, 666–669.

Five fatal cases of esophageal atresia with tracheo-esophageal fistula are reported briefly. The usual roentgen findings are reviewed.

1. Lipiodol, preferably through an esophageal tube, will outline the upper segment (upright position avoids spillage into larynx). Barium should not be used when this condition is suspected.

2. The presence of air in the stomach and bowel in a patient with esophageal atresia indicates tracheo-esophageal fistula, although its absence does not prove lack of fistula, as the opening may be valvular.

3. In all 5 cases here reported the lower esophageal segment joined the trachea within 1 cm. of the bifurcation. Using this indirect method, an estimate of the gap can be made, if air does not outline the two segments.

4. Lungs may show collapse, or consolidation secondary to aspiration.

5. Other abnormalities should be noted.

The author urges earlier diagnosis and surgery; very few survivors of this condition are reported in the English literature.—*Martha E. Mottram, M.D.*

Schneider, Martin, and Klein, C. P. Blast injury of the lungs with report of a case occurring in peace time. *Radiology*, April, 1950, *54*, 548–553.

The etiology, pathogenesis and pathology of blast injuries to the lungs is presented. An explosion produces a radially extending wave of increased pressure which compresses the chest and ruptured alveolar capillaries. Disruption of the alveoli does not occur. Ruptured ear drums and hemorrhage from abdominal viscera may accompany pulmonary injury

A patient who received pulmonary injury without local, external or bony trauma in the Texas City disaster is discussed. He manifested otorrhea, renal hemorrhage and pulmonary hemorrhage. Seven chest roentgenograms following pulmonary changes are presented.—*E. E. Seedorf, M.D.*

Mordasini, E. R., and Sighart, H. Beitrag zum Problem des unvollständigen Pneumothorax. Die Kaolinverödung der Pleuraraumes. (Contribution to the problem of incomplete pneumothorax; the obliteration of the pleural space with kaolin.) *Schweiz. med. Wchnschr.*, April 15, 1950, *80*, 386–392.

The authors base their theory on the fact that an incomplete pneumothorax gives poor results and often damages the lower lobe which is usually uninvolved in early tuberculosis. Such an incomplete pneumothorax often leads to severe pleural effusion and empyema later necessitating decortication.

To avoid these complications the authors recommend that an incomplete pneumothorax be given up within the shortest time, best within a few days, although it was found that even an incomplete pneumothorax of short duration not infrequently leads to marked improvement of the tuberculous process and a reduction in the size or complete disappearance of cavities, as demonstrated by clinical and roentgenological examination.

In order to improve the effectiveness of the collapse therapy in cases of incomplete pneumothroax, the authors attempted to obliterate the pleural space with injection of kaolin.

The results of this procedure were surprising. Complete disappearance of even extremely large sized cavities was noted clinically and by roentgen examination in one-third of the cases, in another third there was marked improvement whereas in the remainder there was no noticeable change.

The authors believe that their method of treatment represents a definite contribution to the betterment of collapse therapy in tuberculosis.—*H. P. Mueller, M.D.*

Spitzer, J. M., Rosenthal, Norman, Weiner, Murray, and Shapiro, Shepard. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis. *Ann. Int. Med.*, Nov., 1949, *31*, 884–888.

The authors state that it is common belief that venous thrombosis and pulmonary embolism are parallel phenomena. As a result of their study of postmortem protocols they failed to find confirmation of this belief. They reviewed the necrospy protocols of two groups of cases. The first group of 184 consecutive miscellaneous autopsy records, excluding those with portal cirrhosis, revealed that the incidence of pulmonary embolism as found at autopsy was 14 per cent. The second group of 97 cases consisted only of patients showing portal cirrhosis at autopsy, and in this group there was no instance of pulmonary embolism. The incidence of cardiac and peripheral venous thrombosis was about the same in both groups. Also, both showed a decreased coagulability of the blood; therefore this factor alone could not, in the author's opinion, influence the formation of pulmonary emboli.—*H. L. Jaffe, M.D.*

Scadding, J. G. Sarcoidosis, with special reference to lung changes. *Brit. M. J.*, April 1, 1950, *1*, 745–753.

This article presents a historical review of this disease and attempts to define sarcoidosis as "that group of cases in which there are generalized changes having a similar histology to that of the skin lesions which the dermatologists have named sarcoids." There is a close resemblance of certain tubercles of tuberculosis, erythema nodosum, brucellosis, and the granulomatous lesions following chronic exposure to beryllium to the noncaseating tubercle of sarcoidosis.

The incidence of the disease, the author believes, varies with the race. In Switzerland an incidence of 0.13 per 1,000 was noted. In the United States there seems to be a higher incidence in the Negro section. A comparative estimate of the various reports would place the disease about 17 times as frequent in Negroes as in white persons.

The incidence of involvement of individual organs varies, with skin lesions most common. About 70 per cent of the cases reported showed intrathoracic changes. An attempt is made to classify the intrathoracic lesions in five groups: (1) enlargement of hilar nodes without detectable lung change; (2) bilateral enlarged nodes with diffuse mottling in the lung; (3) diffuse pulmonary infiltration without gross evidence of hilar lymph node enlargement; (4) fine reticulation; (5) fibrosis emphysema and bulla formation. From the author's experience he does admit that each patient may eventually go through each of these five stages. He feels that if he had the courage of his convictions, he would classify all cases as "noncaseating tuberculosis."

The treatment listed covers the literature, with citation of results from the literature. Roentgen therapy has been of no value. Streptomycin has been used without effect. Calciferol in large doses was used in 9 patients. Six cases tolerated the drug and showed improvement, warranting further trial. —*R. J. Reeves, M.D.*

Weisel, Wilson, Raine, Forrester, and Owen, George C. Acute lung abscess. *Am. Rev. Tuberc.*, April, 1950, *61*, 474–482.

Thirty-five consecutive patients with acute lung abscess were reviewed in an attempt to re-evaluate the results and methods of treatment.

The etiological factors in this group of patients were as follows: bronchial embolism in 17 patients, of which 9 were postoperative; suppurative pneumonitis in 14 patients, pulmonary infarct in 2; and bronchiogenic carcinoma in 2. The last 2 were not included in the study.

All of the studied 33 patients recovered from the acute lung abscess, but 6 patients (18 per cent) had residual pulmonary disease. Three of these 6 patients had bronchiectasis which could have antedated the abscess or may have been the result of it. Three had persistent pulmonary symptoms.

In the total group, 26 patients were treated solely by medical regimen, and 9 patients were treated surgically. The possibility that the 6 of the medically

treated group who have persistent pulmonary disease may require surgery is recognized.

Bronchoscopy was valuable in diagnosis and localization of the disease, and in some cases valuable therapeutically in removing thick plugs of mucus and dilating stenosed bronchi after the acute inflammatory phase had subsided. Penicillin aerosol was considered the most important single factor in medical treatment. It was used in conjunction with parenteral penicillin.

Of the 9 cases treated surgically, 8 showed no evidence of residual disease. One patient who had bronchogenic carcinoma died of metastatic disease.—*Lois Cowan Collins, M.D.*

Abrahamson, S., O'Conner, M. H., and Abrahamson, M. L. Bilateral alveolar lung carcinoma, associated with the injection of thorotrast. *Irish J. M. Sc.*, May, 1950, *6*, 229–235.

A lung tumor believed to be a primary growth of the lung alveoli is described in a patient who, sixteen years previously, had been injected with 75 cc. of thorotrast. At autopsy the spleen and liver were radioactive and were densely outlined on previous films of the abdomen due to the concentration of thorotrast in the reticulo-endothelial system. No radioactivity could be detected in the lungs but they were markedly fibrotic, weighing about three times the weight of a normal lung.

Microscopically the lung alveoli were lined with tall secretory epithelium yielding mucin and papillary projections of epithelium extending to the alveolar spaces. The process was almost evenly distributed throughout every alveolar space in both lungs.

A similar appearance was seen in secretions from the glands and from a nodule in the pancreas, suggesting distant metastases.

The authors quote from the literature a number of reports where thorotrast has induced carcinoma in man and experimental animals. Why the thorotrast from deposits in the reticulo-endothelial system should produce a tumor in the lungs is not explained, however. The tumor was seen to be of a low grade of malignancy without any invasive or destructive characteristics, and it undoubtedly had a multifocal origin in both lung parenchymas simultaneously.

The various theories regarding the possibility of a primary carcinoma developing in the alveolar tissue is also discussed. The fact that the alveoli are lined by epithelium up to the sixth fetal month should be cause enough to act as a precursor to the later development of primary alveolar carcinoma.—*W. M. Roy, M.D.*

Cahan, William G., and Farr, Hollon W. Tracheal aspiration—an additional method for the early diagnosis of carcinoma of the lung; preliminary report. *Cancer*, May, 1950, *3*, 475–480.

A simplified method of obtaining bronchial washings for cytologic examination in early cases of lung carcinoma is described. No. 14 and No. 16 French rectal catheters were employed for the tracheal aspiration. A total of 10 cc. of a solution of equal parts of 1 per cent pontocaine and 0.85 per cent saline was used for the washings. The method was applied in 42 patients. In 11 cases of proved positive classification, the tracheal aspirate duplicted or improved upon the rating of other cytological methods and in 2 cases was the sole determining factor.

The method has the advantage of relative simplicity and ease for both patient and physician. The aspirated material contains less contaminants to hinder the cytologist than specimens obtained by other means.—*W. L. Bridges, M.D.*

Wynder, Ernest L., and Graham, Evarts A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of six hundred and eighty-four proved cases. *J. A. M. A.*, May 27, 1950, *143*, 329–336.

This is a detailed report of the study of 684 cases of proved bronchiogenic carcinoma. The investigation is primarily concerned with findings bearing on the relationship of tobacco smoking. Most of the information was obtained by personal interviews and two control studies were made at the same time to check on possible bias on the part of the interviewers. The authors state that the excessive and prolonged use of tobacco, particularly cigarets, appears to be a significant factor in the development of bronchiogenic carcinoma. Among the cancer patients 51.2 per cent were excessive or chain smokers as compared to 19.1 per cent among the general hospital patients. The presence of carcinoma of the lung in a male nonsmoker is quite rare.

The authors report that 96.1 per cent of patients with carcinoma of the lung who had a history of smoking had smoked for over twenty years. They believe that this is one of the reasons for the greater incidence of this disease among men today.

The studies indicate that tobacco has much less influence on the development of adenocarcinoma than on other types of bronchiogenic carcinoma.

In summary, it may be said that the findings in this detailed study definitely support the opinion that tobacco smoking is an etiologic factor in bronchiogenic carcinoma.—*A. E. Imler, M.D.*

Levin, Morton L., Goldstein, Hyman, and Gerhardt, Paul R. Cancer and tobacco smoking. *J. A. M. A.*, May 27, 1950, *143*, 336–338.

The authors report a study of 1,045 male cancer patients and 605 male non-cancer patients. The entire group of 1,650 patients was used as a standard population. This report indicates that carcinoma of the lung occurs more than twice as frequently

among those who have smoked cigarets for twenty-five years as among other smokers or non-smokers of comparable age. The survey included cancers in all locations and the data suggest a causal relationship between cigaret and pipe smoking and cancer of the lung and lip, respectively.—*A. E. Imler, M.D.*

Sherman, Robert S., and Malone, Bert H. A roentgen study of muscle tumors primary in the lung. *Radiology*, April, 1950, *54*, 507–515.

Attention is called to 7 cases of verified primary muscle tumors in the lung, 3 malignant and 4 benign. These tumors existed as single round areas of increased density varying from 2.5 to 8.5 cm. in diameter. The density was about that of water and was entirely homogeneous. The tumor in each instance was sharply demarcated from the surrounding normal lung and there was no other abnormality in the chest.

A reliable roentgen diagnosis of this type of tumor is not possible but the lesion should be kept in mind when considering round shadows which may be fluid-filled cysts, solitary metastasis or primary carcinoma, tuberculoma, and hamartoma.—*C. A. Stevenson, M.D.*

Stephens, H. Brodie, and Shipman, Sidney J. Pulmonary alveolar adenomatosis. *J. Thoracic Surg.*, April, 1950, *19*, 589–603.

This disease is a specific type of pulmonary tumor, multicentric in origin, showing slow growth and a tendency to reproduce the alveolar structure of the lungs. It may reappear several years later in a different part of the lungs. Delarne and Graham call it alveolar cell carcinoma. Swan proposes the following criteria for the diagnosis of this condition which he calls pulmonary adenomatosis: alveolar cellular proliferation characterized by tall, columnar, mucus-producing cells; absence of an intrinsic tumor of the bronchial tree; and absence of primary adenocarcinoma of any other part of the body. Women are more commonly affected and metastases to regional lymph nodes or distant sites have been reported. A similar condition, Jagziekte, is seen in sheep and is thought to be caused by a virus.

The authors report the case of a woman, aged fifty-one, whose pulmonary symptoms began shortly after a definite, though casual, exposure to a flock of sick sheep. A progressive cough productive of a mucoid and frothy secretion was the main symptom. Roentgen examination showed an area of increased density in the right lower lung field which increased in size during the next two years. Bronchoscopy and sputum studies were negative. On surgery, the right lower lobe was salmon pink in color with a peculiar smooth, solidified surface. Histopathologically this case fitted the diagnosis of pulmonary adenomatosis as proposed by Swan. Seven months following operation an abnormal density appeared in the base of the right lung—no doubt, a recurrence. Discussion of this paper brought out the following points: This disease is not as rare as was thought; 5 per cent of lung carcinomas fall in this category. The thin, watery secretion is quite characteristic and malignant cells can be demonstrated in it. It is not a surgical disease. Antibiotics might be helpful against the possible virus. Pulmonary adenomatosis should be regarded as a primary cancer of the lung of multicentric origin, not arising in a bronchus. A specific response to stimulation by a virus is the most likely etiologic basis.—*F. M. Reis, M.D.*

Anlyan, A. J., Lovingood, C. G., and Klassen K. P. Primary lymphosarcoma of the lung; report of a case. *Surgery*, April, 1950, *27*, 559–563.

This article is a report of a case of primary lymphosarcoma of the lung. Only 4 other cases of this lesion have been reported previously. Routine roentgen examination of the thorax of a man, aged sixty-three, disclosed an abnormal shadow. There was no change in the appearance of the shadow five months later, and he had no cough, thoracic pain, loss of weight, fever or malaise. Percussion of the posterior part of the right side of the thorax disclosed dullness near the base of the lung.

Roentgenographic examination of the thorax disclosed an area of increased density in the base of the right lung posteriorly and near the spinal column. This area of denseness was sharp in outline, homogeneous, and measured 4 by 4 cm. Bronchography revealed partial narrowing of the bronchus supplying the involved part. Bronchoscopy and examination of the bronchial washings did not disclose anything of significance.

The lower lobe of the right lung was removed. Examination of a frozen section of the mass revealed that the lesion probably was a lymphosarcoma. The hilar lymph nodes were not involved, and there was no evidence of metastasis or involvement of the bone marrow and peripheral blood despite the fact that the tumor had been present for at least nine months. —*C. B. Holman, M.D.*

Mathisen, A. K., Morris, W., and Wilson, G. B. The value of miniature radiography in the detection of heart disease. *Am. Heart J.*, April, 1950, *39*, 505–506.

During a two month period the miniature chest films (4 by 5 inches) taken by a tuberculosis detection unit in British Columbia were examined for abnormal cardiovascular shadows. No mention is made of the exact roentgenographic criteria used by the authors in screening the miniature films for evidence of cardiac disease. From a total of 7,093 films, 158 were thought to show cardiovascular abnormality; subsequently these selected patients were examined

clinically and standard films exposed. Ninety persons (1.27 per cent) were then classified as having definite heart disease—hypertensive (42), arteriosclerotic (15), rheumatic (26), congenital (6), and thyrotoxic (1). Thirty-three of this group of 90 were unaware of their existing cardiac disease.

Sixty-eight of the patients recalled for further examination proved to have no detectable heart disease; the high percentage of screening error was attributed mainly to the distortion incident to the short (48 inch) focal-film distance employed in photofluorography.—*Harold Fulton, M.D.*

Kaufman, Paul, and Poliakoff, Harvey. Studies on the aging heart. I. The pattern of rheumatic heart disease in old age (a clinical-pathological study). *Ann. Int. Med.*, May, 1950, *32*, 889–904.

This paper is an elaborate study of 50 cases of rheumatic heart disease from forty to eighty-one years of age, with autopsy records. Roentgenographic findings are not complete and the records are largely clinical. From the roentgen standpoint, the following conclusions seem justifiable: Rheumatic heart disease must be considered in older age groups. Diagnosis can usually be made clinically. Roentgen reports on such cases would appear to be incomplete. In a fourth of the cases rheumtic pattern is replaced by hypertension.—*E. C. Baker, M.D.*

Smith, J. Chandler, and Sancetta, Salvatore M. Healed dissecting aneurysm of the aorta erroneously diagnosed paramediastinal effusion; death following attempted aspiration. *Circulation*, April, 1950, *1*, 792–796.

This is a case report of a healed dissecting aneurysm of the aorta which was not diagnosed but was mistaken for a loculated pleural effusion. Death of the patient was due to an attempted aspiration of the suspected loculated fluid.

The authors admit that the improper diagnosis was made in spite of fairly definite clinical history and physical findings. Perhaps too much emphasis was placed on the roentgen diagnosis which was presumably made without benefit of accurate clinical history.

The preliminary paragraph with reference to dissecting aneurysms is a concise review of a subject covered by the case report. The author states that 1 per cent of dissecting aneurysms of the aorta develop re-entry tears and heal, forming the so-called double-barrelled aorta, with which patients are sometimes able to live for long periods of time.—*R. E. Kinzer, M.D.*

Friedlander, Saul, Hein, Gordon E., and Siemens, John C. Primary myosarcoma of the heart; report of a case associated with malignant carcinoids and pancreatic heterotopia. *Circulation*, April, 1950, *1*, 797–804.

Primary striated muscle sarcomas are extremely rare and the authors present their case which would presumably be the ninth reported case. They do not say with certainty that the tumor arose in the heart.

Although their patient was under observation for a period of nine and a half months before his death, the correct clinical diagnosis was not made.

In retrospect, the clinical picture of precordial pain, discovery of bone metastases, with the development of a mass in the left chest might have lead to the proper diagnosis. The changing murmurs and transient arrhythmia might have led them to suspect that they were dealing with a rare heart tumor. Instead, the more common diagnosis of carcinoma of the bronchus was entertained.

The autopsy findings are reported in fairly great detail and a summary is made of the findings in previously reported cases of striated muscle sarcoma of the heart.—*R. E. Kinzer, M.D.*

Hochberg, Lew A., and Robinson, Alexander I. Primary tumor of the pericardium involving the myocardium: surgical removal. *Circulation*, April, 1950, *1*, 805–808.

A brief summary of this case is presented in the opening paragraph. The case is that of a child who presented a large smooth circular mass along the right heart and mediastinal borders with extension anteriorly and downward as far as the dome of the diaphragm. A preoperative diagnosis could not be definitely made.

On examination of the mass at the time of operation it was found that the tumor connected to the heart muscle as well as to the pericardial sac. The thymus was also connected to the tumor mass. In removing the tumor it was necessary to shave off a small portion of heart muscle as well as a small part of the thymus gland.

The patient had an uneventful postoperative course and has remained well for eighteen months after operation. The pathologic diagnosis was cavernous hemangioma.—*R. E. Kinzer, M.D.*

Heyer, Howard E., Poulos, Ernest, and Acker, Julian H. Electrokymographic studies in insufficiency of the aortic and pulmonic valves. *Circulation*, April, 1950, *1*, 1037–1048.

With the aid of the electrokymograph, the authors have studied the border motion of the great vessels in a group of patients. These included 30 normal subjects, 22 patients with aortic insufficiency, 1 with tetralogy of Fallot complicated by pulmonary insufficiency and 2 with aortic stenosis in association with aortic insufficiency. They found that the electrokymograph provided an easy, accurate

method of studying circulatory dynamics. The tracings of the great vessels with insufficient valves revealed a characteristic contour. The most striking alteration was the abolition of or marked diminution in the incisural marking which is normally present in the descending limb of the electrokymographic tracing and which is synchronous with closure of the aortic valves. In addition they noted (1) rapid decline in volume in early diastole, (2) alterations in the general shape and contour of the aortic tracing, (3) prolongation of the ejection phase and (4) variation in the normal ventricular filling pattern of the left ventricle. In patients with a parasternal diastolic murmur, the electrokymogram may be of great help in determining the exact site of origin of the murmur, whether aortic or pulmonic.—*Gerald Lavner, M.D.*

Dack, Simon, Paley, David H., and Sussman, Marcy L. A comparison of electrokymography and roentgenkymography in the study of myocardial infarction. *Circulation*, April, 1950, *1*, 551–563.

Until the advent of electrokymography, roentgen kymography provided the only simple method of recording roentgenographically the movement of the cardiac borders during the cardiac cycle, and thus aiding in the detection of localized areas of myocardial damage and infarction. The use of roentgen kymography has not become widespread because of certain inherent limitations of the method. Insufficient magnification of ventricular movement makes accurate recording difficult. Technically, since only one or two cycles can be recorded, it has limited usefulness in patients with arrhythmias or bradycardia.

These disadvantages are overcome by the use of electrokymography. Cardiac movement is magnified and recorded in graphic form similar to a pulse curve. This permits easier analysis of the movements of the cardiac borders. Furthermore, as many cardiac cycles may be recorded as safety of the fluoroscopic procedure will allow. Perhaps of greatest importance, electrokymography lends itself easily to simultaneous recording of cardiac movement, the electrocardiogram, carotid and venous pulse tracing, phonocardiogram and cardiac apex beat. This permits a correlation of the events which occur during the cardiac cycle and a more accurate comparison of various segments of the cardiac borders.

Two cases of myocardial infarction are reported in both of which electrokymography presented clear-cut evidence of infarction which was not evident on roentgen kymographic study.—*Gerald Lavner, M.D.*

Baer, Samuel, Behrend, Albert, and Goldburgh, Harold L. Arteriovenous fistulas of the lungs. *Circulation*, April, 1950, *1*, 602–612.

Arteriovenous fistulas of the lung may be clinically confused with such conditions as polycythemia vera and congenital heart disease. It is important to diagnose these fistulas as there is a risk of severe hemorrhage which may be fatal, and the lesion is amenable to surgery.

The clinical manifestations result from shunting of anoxemic blood from pulmonary artery to vein without going through the pulmonary alveoli and consist of polycythemia, cyanosis, and clubbing of fingers. Dyspnea is an outstanding symptom.

The diagnosis can be made by roentgenogram. These are characteristic circular, cylindrical, or nodular lesions in the lung. The lesions are non-progressive. They may pulsate. Planigraphic studies have helped by showing some of the larger vessels from the hilus, extending to the parenchymal lesion. Angiocardiogram has also been successfully used. Roentgen kymography may differentiate the lesion from non-vascular shadows.

A case is reported and 24 previously reported cases reviewed.—*Joseph Levitin, M.D.*

Sancetta, Salvatore M., and Zimmerman, Henry A. Congenital heart disease with septal defects in which paradoxical brain abscess causes death; a review of the literature and report of two cases. *Circulation*, April, 1950, *1*, 593–601.

Brain abscess is a possible complication in patients with a cardiac septal defect. There is a chance shunting of organisms and infected material from the venous to the arterial circulation through the septal defect without the benefit of pulmonary filtering. The diagnosis should be suspected in patients with known congenital septal defects who have symptoms of central nervous system involvement.

Two cases are reported and the 42 other cases reported in the literature are reviewed.—*Joseph Levitin, M.D.*

MacGilpin, Harold H., Jr. Truncus arteriosus communis persistens. *Am. Heart J.*, April, 1950, *39*, 615–625.

The truncus arteriosus communis persistens is a single large arterial trunk, approximately the size of the usual aorta and pulmonary artery combined, arising from the base of the heart, guarded by two, three, or four valve cusps. It functions as aorta and pulmonary artery and thus gives rise to the coronary, systemic, and pulmonary circulations. The anomaly is classified as "complete" when the pulmonary arteries arise separately from the common trunk, or when the sixth aortic arch structures (pulmonary arteries and ductus arteriosus) completely fail to develop, blood reaching the lungs through collateral channels (mainly the bronchial arteries). In the "partial" type, an incomplete septum separates the truncus and a short pulmonic trunk which gives off one or two pulmonary arteries and occasionslly a ductus arteriosus. In both the complete and incomplete types there is an associated high ventricular

septal defect; the truncus may override the septum, or in extreme cases arise entirely above the right ventricle.

There are five distinct patterns which the pulmonary circulation might adopt with truncus arteriosus communis: (1) common pulmonic trunk with patent ductus arteriosus; (2) common pulmonic trunk without patent ductus areteriosus; (3) separate origin of the right and left pulmonary arteries from the truncus; (4) a pulmonary artery to one lung, the other lung being supplied by collaterals; (5) absent pulmonary arteries, lungs supplied completely by collaterals. The collected cases (55) from the literature are classified by the author according to these five types of pulmonary blood supply.

The case presented concerns a thirty-five year old woman with continual cyanosis since birth, but who had led a fairly active life until her terminal illness. Fluoroscopy and roentgenograms of the chest revealed an enlarged heart with the left and right ventricles participating in the enlargement, the pulmonary conus prominent, but no increased lung vascularity. The aorta appeared to arise farther to the right than normally and contained calcific areas in its ascending portion. A diagnosis of multiple congenital defects was made. Postmortem examination showed a partial truncus (type 4) in which the right pulmonary artery failed to develop.

It is emphasized that the truncus anomaly is compatible with a fairly long life and that the roentgen findings of truncus arteriosus so characteristic in infants and children may not be present in the adult.—*Harold Fulton, M.D.*

Miller, A. J., Prec, O., Akman, L., Katz, L. N., and Gibson, S. A case of congenital heart disease; truncus aorticus solitarius, single ventricle, and aberrant coronary drainage into the common ventricle. *Am. Heart J.*, April, 1950, *39*, 607–614.

The case of a five and one-half year old, well developed white female is presented in detail. The child exhibited slight cyanosis and dyspnea on exertion; there were no audible heart murmurs. Fluoroscopy and roentgenograms revealed an extremely wide heart base as seen in the anteroposterior position. A large aorta was present on the left. The left hilus appeared as a rounded well defined density; the right hilus was not seen.

During right heart catheterization, the catheter passed easily into the right ventricle area and then passed unopposed on to the left border of the heart, suggesting a common ventricle. The pulmonary artery could not be located by catheter. Additional evidence of the presence of a single ventricle was the similarity of oxygen content of the blood from several areas in the ventricular cavity (average value 16.1 volumes per cent) to that of the femoral artery blood (16.9 volumes per cent). An aberrant vessel entering the left side of the ventricle was accidentally entered and was found to show a very low pressure gradient and extremely low oxygen saturation, indicating that it carried venous blood, probably from the myocardium.

Angiocardiography revealed a functionally single ventricle with only one vessel arising from the heart, probably the aorta. The left pulmonary artery arose from the upper descending aorta; the right pulmonary artery was not visualized, the circulation to the right lung being presumably by way of bronchial arteries.

Apparently this particular combination of anomalies of the aorta and pulmonary arteries has been reported only once previously, and is classified as a truncus aorticus solitarius ("pseudo" truncus arteriosus) with left pulmonary artery arising from the descending aorta. In addition, an aberrant coronary vein or sinus entered the left side of a common ventricle.—*Harold Fulton, M.D.*

Freeman, Norman E., Miller, Earl R., Stephens, H. Brodie, and Olney, Mary B. Retrograde arteriography in the diagnosis of cardiovascular lesions. II. Coarctation of the aorta. *Ann. Int. Med.*, May, 1950, *32*, 827–841.

The technique of retrograde arteriography into the left common carotid artery for the purpose of visualizing the aorta in coarctation is carefully described. This examination was of diagnostic import in 13 of 15 patients. Case histories of these 13 cases are presented. Two cases had a normal upper thoracic aorta. One case had narrowing of the aorta in the region of D_{11} to L_1. Because of location this patient was not operated upon. There was one case with narrowing of the aorta, insufficient to justify surgery. One case showed marked dilatation of the left subclavian artery with no demonstration of the thoracic aorta. Eight cases showed coarctation and were deemed suitable for surgery. Following surgery 6 of these cases were returned relatively to normal and there were 2 postoperative deaths. The single complication of these examinations was a hematoma in the wound of the neck. This paper gives the cardiac team one more diagnostic aid.—*E. C. Baker, M.D.*

Gross, R. E., Neuhauser, E. B. D., and Longino, L. A. Thoracic diverticula which originate from the intestine. *Ann. Surg.*, March, 1950, *131*, 363–375.

The authors present 3 cases of elongated diverticula, arising from the duodenum or jejunum, penetrating the right side of the diaphragm, and presenting in the chest as hollow gas or fluid-containing structures. Parts of such side arms had the size and appearance of loops of bowel, but in places they

ballooned out to make a large structure. All reached to the apex of the lung and were covered by parietal pleura. In 2 cases, the diaphragmatic defect was small; in 1 case the opening was large enough to permit herniation of several loops of ileum up into the chest, alongside the diverticulum.

The diverticula had smooth muscle coats and were lined by mucosa resembling some portion of the alimentary tract. In 1 case, the lining was similar to that of the jejunum, colon, and the respiratory tract; in the other 2 cases it resembled gastric mucosa, this being found to secrete hydrochloric acid and pepsin.

nize, or at least suspect, this abnormality, if they encountered it again. In the first patient (Fig. 1), loops of intestine containing air and gas were seen above the diaphragm, to the right of the heart shadow, which led to a diagnosis of a diaphragmatic hernia (which the patient had). After surgical reduction of the diaphragmatic hernia, some air-filled loops could still be seen on the right side of the chest (which on subsequent operations were shown to be due to the presence of the elongated and coiled diverticulum which remained in this area). In all 3 cases, there was some sort of mass extending out

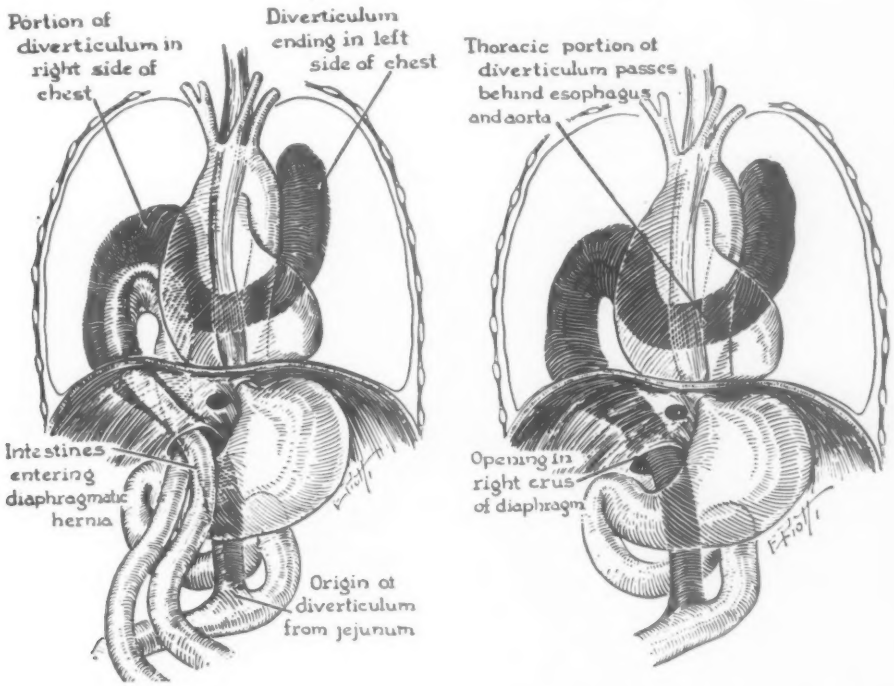

Portion of diverticulum in right side of chest
Diverticulum ending in left side of chest
Intestines entering diaphragmatic hernia
Origin of diverticulum from jejunum
Thoracic portion of diverticulum passes behind esophagus and aorta
Opening in right crus of diaphragm

Fig. 1. Thoracic diverticulum originating from the jejunum, associated with diaphragmatic hernia (Case 1). *Left:* Sketch showing loops of intestine above the right diaphragm and the long jejunal diverticulum ending near the left apex. *Right:* Same case, after surgical reduction of the diaphragmatic hernia showing the intrathoracic course of the long jejunal diverticulum. (Reproduced by permission from the *Annals of Surgery*, March, 1950, *131*, 363–375.)

The symptomatology was referable to: (1) the accumulation of gas or material within the thoracic portion of the diverticulum, producing respiratory disturbances; (2) the formation of hydrochloric acid and pepsin within the diverticulum, causing ulceration in the neck of the diverticulum or nearby intestine, with hemorrhage from the alimentary tract; (3) the accumulation of very acid (pH 3.9) material within the diverticulum, producing an intense reaction in its wall and in regional structures, so that chest pain appeared.

The roentgen findings were not diagnostic of the condition, but there were certain features which the authors felt would probably permit them to recog-

from the mediastinum, usually to the right, which had the appearance of a long, narrow structure, contiguous to and running along the mediastinum, or it had a more bulbous and rounded shadow projecting out prominently from some part of the mediastinum. Because of obscuration by the normal cardiac or mediastinal shadows, it was not always possible to visualize the entire intrathoracic part of the narrow diverticulum. Conversely, when the diverticulum had a large diameter, it could be seen to encroach upon the pleural cavity and to extend from the diaphragm to the apex of the chest. In one instance, this mass was very large and had a central indentation (produced by the azygos vein) which gave it a dumb-

bell shape. The shadows were opaque if the diverticula contained fluid, but in some instances they were radiolucent whenever gas became pocketed in the pouch. It was of value to have film studies with the patient in an upright position, to detect any tiny bubbles of gas, which were missed when film exposures were taken with the patient in a supine position. In only one instance did barium pass into the diverticulum during contrast study of the alimentary tract. Solid thoracic shadows might suggest neoplasm, teratoma, or a gastrogenous cyst (duplication) of the esophagus. It has been the experience of the authors that most duplications of the esophagus do not communicate with the esophagus and hence do not contain gas. Therefore, the finding of air in a cystic structure projecting from the mediastinum tended to make them think more of a diaphragmatic hernia or of a diverticulum of the small intestine which projects into the thorax, such as they report herewith.

The surgical treatment of these abnormalities might lead the surgeon on a long therapeutic course, requiring several operative procedures, or it might be possible to remove the entire lesion at one sitting. If the lesion is suspected, the authors feel that a combined thoracic-abdominal exploration through posterior thoracic and right flank exposures will enable a one-stage removal of the lesion. This was done in one of the cases reported, the patient withstanding the extensive procedure very well. Possibly, it is not necessary to remove all of the diverticulum in each case where this malformation is found. When the symptoms are due entirely to the accumulation of fluid and gas within the intrathoracic portion of the diverticulum, it is probably sufficient to excise only that part which lies above the diaphragm. When, however, the diverticulum is lined by gastric mucosa which secretes hydrochloric acid and pepsin, so that there is severe chest pain, or when there is intestinal hemorrhage, it becomes highly desirable to remove the entire diverticulum, if this is technically possible.

The article is accompanied by sketches showing the origin and distribution of the diverticula. One of them crossed from the right side to the left side of the thoracic cavity above the diaphragm, behind the heart.—*T. J. Wachowski, M.D.*

Dubary, Louis. La superposition des coupes tomographiques du poumon. (Superimposing of tomograms of the lung.) *Presse méd.*, April 15, 1950, *58*, 415.

To prevent errors and mistakes in the interpretation of tomograms of the lung—especially in the diagnosis of irregular cavities—the author suggests the simple method of placing the tomograms made at different levels upon each other and viewing them. In the case of irregular cavities where each tomographic section shows only a portion of the lesion the superimposition of two tomograms (made for example at 8 and 10 cm. from the posterior thorax) will aid greatly in correctly outlining the margins and walls of the lesion. A brighter source of illumination than provided in the ordinary view-box will be required, of course, but such lamps are usually at hand for studying deliberately overexposed films.—*W. M. Loehr, M.D.*

Abdomen

de Gennes, L., May, J.-P., and Simon, G. Le rétropneumopéritoine (nouveau procédé d'exploration radiologique de l'abdomen). (Retropneumoperitoneum; a new procedure for roentgenologic investigation of the abdomen.) *Presse méd.*, April 5, 1950, *58*, 351–352.

The authors present a comparative study of advantages and disadvantages in the use of pneumoperitoneum and pneumokidney in roentgen examination of subdiaphragmatic viscera and point out why preference should be given to their technique of *retropneumoperitoneum*. It is performed through the precoccygeal route. The patient is in the knee-chest position, and after sterilization of the skin, a short needle (*not over* 4 cm. in length and of the caliber used in intramuscular injections) is inserted 1 cm. anterior to the tip of the coccyx and in the anococcygeal line, and pushed a little obliquely in such a way that it will strike the tip of the coccyx. When the bony contact is established the needle is displaced just enough to clear the tip of the coccyx. The contact with the coccyx is necessary for the injection *must be made above* the anococcygeal raphé which offers no abnormal resistance to the needle. Bony contact with the tip of the coccyx permits one to know the needle is above the anococcygeal raphé, and this raphé is avoided if one goes 1 cm. anterior to the coccyx. With the needle in place, oxygen is injected by a pressure device such that in about three minutes 1,000 to 1,200 cc. (according to the size of the patient) is administered. During the injection it is necessary to determine that no *perineal emphysema* occurs which is sought for by its characteristic crepitation and that the lumbar fossae become tympanitic to percussion which is the criterion of a correct retropneumoperitoneum. The patient is then placed in a semirecumbent position for one hour. At the end of this time standard films are made in several views (oblique lateral, lateral decubitus, upright, etc.) as may be desired. The best films are obtained one to two hours after the injection. Four hours afterward they become less distinct and diagnostic; twenty-four hours afterward most of the gas has disappeared and forty-eight hours after injection not a trace of gas remains. The authors have had no serious accidents with this method in three months of daily use at Hôpital Broussais. Patients have been of all types—cachectic, patients with ascites, hypertension, Addison's disease, renal cancer, leukemia, etc., and the

procedure has been accomplished without accident.

With this procedure the authors claim better visualization of the adrenals than with any other procedure and they feel that it combines the advantages of pneumokidney and pneumoperitoneum without their disadvantages. The method may, when necessary, be combined with other contrast methods, i.e., urography.

There are 6 roentgenograms reproduced illustrating types of lesions visualized by this method.—*W. M. Loehr, M.D.*

Cantor, Meyer O. Radiological criteria for removal of intestinal decompression tube. *Radiology*, April, 1950, *54*, 535–540.

The problem of the correct time to remove an intestinal decompression tube has usually been handled by clamping the tube for various periods of time and then observing the patient to see whether or not distention or cramps occur. The author believes that a more accurate method is to inject 30 to 100 cc. of a thin barium suspension and then follow it by fluoroscopy and roentgenograms for a period of twenty-four hours.

The tube should be clamped for the first five hours in order to prevent withdrawal of the barium. If complete obstruction exists there will be definite puddling of the barium at the site of the obstruction. When partial obstruction exists some puddling will occur but a small amount of barium will pass through. Twenty-four hours should be allowed to determine whether an obstruction is complete or not. When no obstruction exists the barium will be in the colon in about five hours or less.—*C. A. Stevenson, M.D.*

Gottlieb, Charles, Chu, Florence, and Sharlin, Herbert S. Perforation of a gastric ulcer associated with intracranial hemorrhage in a newborn infant. *Radiology*, April, 1950, *54*, 595–597.

A case of perforation of a gastric ulcer in a newborn infant is reported. Dark red stools were passed on the second post-natal day and the baby vomited dark brown fluid. Roentgenographic examinations done on the second and third days revealed a large filling defect in the cardiac end of the stomach and free air under the diaphragm. Diagnosis of perforated hollow viscus was made.

On operation a perforation 3 cm. long surrounded by a necrotic ulcer 0.5 cm. in width was found in the cardiac end of the stomach. A large food clot, plugging the perforation, corresponded to the filling defect seen on the roentgenogram. Death occurred sixteen hours after surgery on the fourth day of life. Autopsy revealed intracranial hemorrhage due to a tentorial tear.

It is emphasized that perforation of a gastric ulcer in a newborn is rare and that diagnosis is difficult.—*A. W. Sommer, M.D.*

State, D., Gaviser, D., Hubbard, T. B., and Wangensteen, O. H. Early diagnosis of gastric cancer. *J.A.M.A.*, April 15, 1950, *142*, 1128–1133.

In order to make an early diagnosis of cancer of the stomach patients have to be studied before they present gastric symptoms. Therefore, the authors selected the following groups as possibly harboring gastric cancer: patients over fifty with achlorhydria and hypochlorhydria after administration of histamine phosphate; patients with pernicious anemia; relatives of patients with gastric cancer; patients with unexplained low hemoglobin levels, or with occult blood in stools. Persons falling into these groups have been surveyed by means of gastrointestinal studies and in some cases gastroscopic examination. From July 1, 1945, to May 1, 1949, 3,921 persons were studied with gastric analysis. Of this group 1,832 had gastrointestinal roentgen examinations, and 7 carcinomas and 32 gastric polyps were found. In addition, 2 gastric carcinomas were missed and 1 misinterpreted.

Ninety-four patients with pernicious anemia had gastrointestinal examinations and 3 gastric carcinomas and 4 gastric polyps were found.

Roentgen examination of 81 relatives of patients with gastric carcinoma, of 62 persons with unexplained low hemoglobin, and of 87 patients with occult blood in stool, showed no gastric neoplasm.

At the Cancer Detection Center in studying 1,715 persons over the age of forty-five, twenty silent neoplasms have been found, of which one was a gastric carcinoma.

The authors believe that it is possible and practical to survey large groups of persons in an effort to uncover early silent carcinomas.—*F. B. Markunas, M.D.*

Edwards, Harold C. Carcinoma of the stomach. *Brit. M. J.*, April 29, 1950, *1*, 973–978.

The belief is widespread that cancer of the stomach is less amenable to surgical cure than cancer occurring in most other situations in the body. However, there are certain things which encourage one to view the prospect, not with gloom, but with hopefulness. It should be asked, "Is cancer of the stomach in its early stages curable? Is it possible to diagnose it before it has passed beyond the bounds of cure by operation?"

There is little if any evidence that cancer of the stomach spreads on the average any more quickly than does, say, cancer of the breast, or that it metastasizes sooner. There is indeed every reason for thinking also that it is as easily eradicated by opera-

tion at a comparable stage of the disease, for the glandular spread is certainly no wider. And even if the liver is more in the path of spread in cancer of the stomach than in cancer of the breast, skeletal and thoracic secondary deposits are far less common.

It can be taken as axiomatic that gastric symptoms arising for the first time in previously healthy patients of the cancer age always have an organic cause and that the commonest cause is cancer, and that secondary anemia at the cancer age must have a primary cause and that cancer of the stomach is one of them. The fact that ancillary diagnostic methods give negative results does not in any way disprove these statements. It is merely evidence that these methods are unable to reveal the cause. They do not remove it; and the clinician should insist on discovering it, even to the point of insistence upon exploratory operation.

It has been the author's experience, that, by the time the radiologist is in a position to say that an ulcer of the lesser curve or prepyloric region is malignant beyond doubt, the growth has passed the stage in which there is probability of cure. Though the growth may be "operable" in the sense that all disease apparent to the naked eye may be eradicable, the prognosis is poor, and may be compared with that of late cases of carcinoma of the breast in which there is involvement of the overlying skin and enlarged axillary glands. The radiologist, in fact, is often made to carry too heavy a responsibility—more than is justified by the ability of roentgenography to diagnose with assurance cancer at an early stage. And in the final analysis the real responsibility is the clinician's, who ought to regard radiology as only one, and not the only one, of the sources of information guiding his actions.

Gastroscopy may be invaluable, though it is not consistently reliable, and negative findings are not conclusive. Its value is probably not so much in differentiating between a simple and a malignant ulcer, as in defining the presence of a lesion missed roentgenologically, or in confirming the presence of a lesion when the roentgen findings are in doubt.

The blood picture, as Osler and McCrae pointed out fifty years ago, follows no recognizable pattern. The importance of blood examinations is not in differential diagnosis so much as that the presence of an otherwise unexplained secondary anemia should lead to an investigation of the stomach as being a possible site of its cause.

Absence of free hydrochloric acid is in favor of a diagnosis of cancer, but its presence, as is well established, is not to be regarded as evidence against cancer. Of more significance than the acid values is the finding of fresh blood in the residuum.

Peritoneoscopy is of no value for early diagnosis, but may, by determining the presence of metastases, be instrumental in saving the patient from unnecessary major surgery. Of greater usefulness is the microscopical examination of fragments obtained from gastric lavage or aspiration when a positive result is diagnostic. The recent smear technique as developed for the cytological diagnosis of uterine cancer offers great possibilities.

The case for routine total gastrectomy in growths of the distal portion of the stomach is not proved, and it is recommended that a portion of the stomach should be left so that the cardia remains intact.—*E. J. McDonald, M.D.*

Majno, G. Du diagnostique précoce du carcinome gastrique; problèmes de pathologie. (Early diagnosis of gastric carcinoma; pathological problems.) *Schweiz. med. Wchnschr.*, April 29, 1950, *80*, 444–452.

Because of the technical difficulties involved, the author believes that mass survey of all adults above the age of fifty in an attempt to detect early gastric carcinoma is impractical. Instead, he proposes that precancerous conditions of the stomach as well as gastric functional disturbances be studied as to their possibility of developing into gastric carcinoma.

He discusses various types of gastritis both hypertrophic and atrophic and concludes that the types most commonly encountereed do not seem to lead to gastric carcinoma. There is, however, one type of gastritis, characterized by an area of polypoid hypertrophy surrounded by atrophic gastritis, which may result in malignant degeneration.

Achlorhydria is often encountered in gastric carcinoma; in many cases, achlorhydria has preceded gastric carcinoma by many years. It is therefore suggested that all patients showing achlorhydria be checked for the possible development of gastric carcinoma.

Mucus normally protects the gastric mucosa from the action of carcinogenic substances. Whenever the secretion of mucus has markedly decreased, periodical examinations should be carried out to detect a possible early carcinoma.

There is a higher incidence of carcinoma in pernicious anemia and these patients should also be followed up.

The author believes that some gastric ulcers do degenerate into carcinoma. If an ulcer suddenly changes its pattern or if it fails to show a tendency to heal under treatment, carcinoma should be suspected. The possibility of an ulcer becoming malignant is greater than that of a carcinoma "in situ" becoming an ulcer; therefore, in most cases the ulcer must be regarded as having been the primary lesion.

Gastric polyposis is also considered to be a premalignant condition.

The author believes that the cytological examination (Papanicolaou) is unreliable in cases of gastric carcinoma. "Gelfoam" surface biopsies through the gastroscope are of greater aid and should be used more extensively.—*Jean-Pierre Jean, M.D.*

Wenzl, M. Magenbeschwerden als Fernsymptom bei Bronchuskarzinom. (Stomach complaints as distant symptoms in carcinoma of the bronchus.) *Wien. klin. Wchnschr.*, April 14, 1950, *62*, 261–265.

The possibility of carcinoma of the bronchus should always be kept in mind in individuals of a certain age group, by the physician who first sees the patient, even in the presence of minor lung complaints. About 20 per cent (72 of 225) of the author's patients with carcinoma of the bronchus had complaints referable to the stomach. In 5 per cent of the patients, these complaints predominated those referable to the lungs and made considerably more difficult the diagnosis of a pulmonary process.

Of the 72 patients with stomach complaints, 18 were studied thoroughly. In 6 of the 18, stomach symptoms were so prominent that little or no significance was attached to the lung complaints. In all of the above 18 cases posterior mediastinal tumor extension and extensive posterior mediastinal lymph node metastases were demonstrated either by operation or autopsy.

The structures situated in the posterior mediastinum, because of extension of the primary process or because of lymph node metastases to that area, may be affected by a lesion arising in the lungs. Pressure upon the vagus or sympathetic nerves may produce irritative symptoms in organs outside of the chest. This has been demonstrated by Neumann in the case of tuberculous mediastinal lymph nodes. The author claims that the stomach symptoms noted in his cases of carcinoma of the lung are remote symptoms from the mediastinal involvement. Roentgen study of the stomach showed no suggestion of any anatomical abnormality; however, as might be expected theoretically, there was an increase in tone, peristalsis, and secretion. An increase in tone of the vagus nerve can produce stimulation of the muscle processes in the stomach.

When mediastinal involvement exists, there also may be atony of the stomach and even paralytic ileus. From various published animal experiments, it appears that stimulation of the vagus nerve, under certain circumstances, can produce a decrease in tone and motility of the stomach. On the other hand, some experiments have shown that stimulation of the splanchnics produces decrease in tone and peristalsis of the stomach as well as an increase in tone of the pylorus. On the basis of the author's studies, it is claimed that mediastinal involvement first stimulates the vagus. Later, should there be paralysis of this nerve by inflammation or tumor, it is possible that the depressing action of the splanchnics may be manifested by decrease in tone and motility of the stomach.

Of particular interest is a relative and absolute lymphocytosis, where previous normal lymphocyte counts existed, in the presence of a demonstrable increase in tone of the vagus nerve. The above findings were established in practically all of the author's cases.

The presence of stomach symptoms in a patient with carcinoma of the bronchus may be significant pre- as well as postoperatively. If these symptoms occur before operation, one may assume that the primary tumor is closely associated with the posterior mediastinum and/or that posterior mediastinal lymph node metastases are present; if the symptoms occur postoperatively, then one must consider the possibility of tumor recurrence in the posterior mediastinum.

In 15 other cases of carcinoma of the bronchus, the author could demonstrate anatomically stomach or duodenal ulcers. These could be incidental findings. Yet, in all of these cases, definite carcinomatous mediastinal involvement was noted. In all but 2 of these cases, the primary tumor was in the right lower lobe. As support of the neurogenic theory as a cause of peptic ulcer is the observation that, in many of the patients, an exacerbation of ulcer symptoms occurred after the lung symptoms appeared (pressure upon vagus nerve).

There are also stomach symptoms in the post-pneumonectomy period in the patients with displacement of the mediastinum due to adhesions. These stomach symptoms are the same as those described earlier in patients with posterior mediastinal involvement. The displacement of the mediastinum need not be the cause of the symptoms. Mayer and Ehler have studied the esophagus in post-pneumonectomy patients and in several with considerable displacement of this organ no clinical symptoms were noted. The author believes that the general shrinking process allows the mediastinal organs to accommodate themselves in their new location. However, the vagus may be bound down by adhesions and be the cause of the patient's complaints. Perigastric adhesions may produce similar symptoms.—*Samuel Richman, M.D.*

Hess, Walter, and Rütte, Bernhard. Die intermittierende und perforierende Pancreascyste. (Intermittent and perforating pancreatic cysts.) *Schweiz. med. Wchnschr.*, May 6, 1950, *80*, 476–479.

A phenomenon which is practically exclusive to the pancreatic cyst is its spontaneous disappearance, followed by reappearance in a few days. This occurs apparently in about 10 per cent of cases.

Clinically, the pancreatic cyst may pursue three different courses: (1) sudden single disappearance with complete spontaneous healing; (2) single disappearance, followed by severe and usually fatal manifestations of perforation of the cyst; (3) frequent fluctuation in size to complete disappearance. In some, however, there is an early recurrence of the cyst: the so-called *intermittent pancreatic cyst.*

It is difficult to explain the spontaneous diminution in size of the cyst. Of the 26 cases found in the literature, 4 probably had perforated into the bowel. In the majority of cases, there is no explanation for the disappearance of the cyst. Recent reports claim that emptying occurs through Wirsung's duct. This process is not a continuous one, but begins only after a certain amount of pressure is built up within the cyst. The location of the cyst in the pancreas has no relationship to its spontaneous fluctuation in size. Of the 20 ruptured cases reported in the literature, 6 were into the duodenum, 2 into stomach, and 1 into both stomach and colon. Six of the above 9 patients died of hemorrhage. Of 10 known cases of rupture into the peritoneal space, 7 died. The complication of rupture of a pancreatic cyst may be expected in about 5 per cent of all cases.

The author presents 1 case demonstrating perforation and 1 of spontaneous diminution in size of a pancreatic cyst. In the latter, the phenomenon occurred three times within a period of seventeen days.

In summary, pancreatic cysts are characterized by temporary regression. This occurs by perforation mostly into the pancreatic duct, and less frequently into the intestine, peritoneum, or into the urinary tract.—*Samuel Richman, M.D.*

Marcuse, Peter M., and Stout, Arthur Purdy. Primary lymphosarcoma of the small intestine; analysis of thirteen cases and review of the literature. *Cancer*, May, 1950, *3*, 459–474.

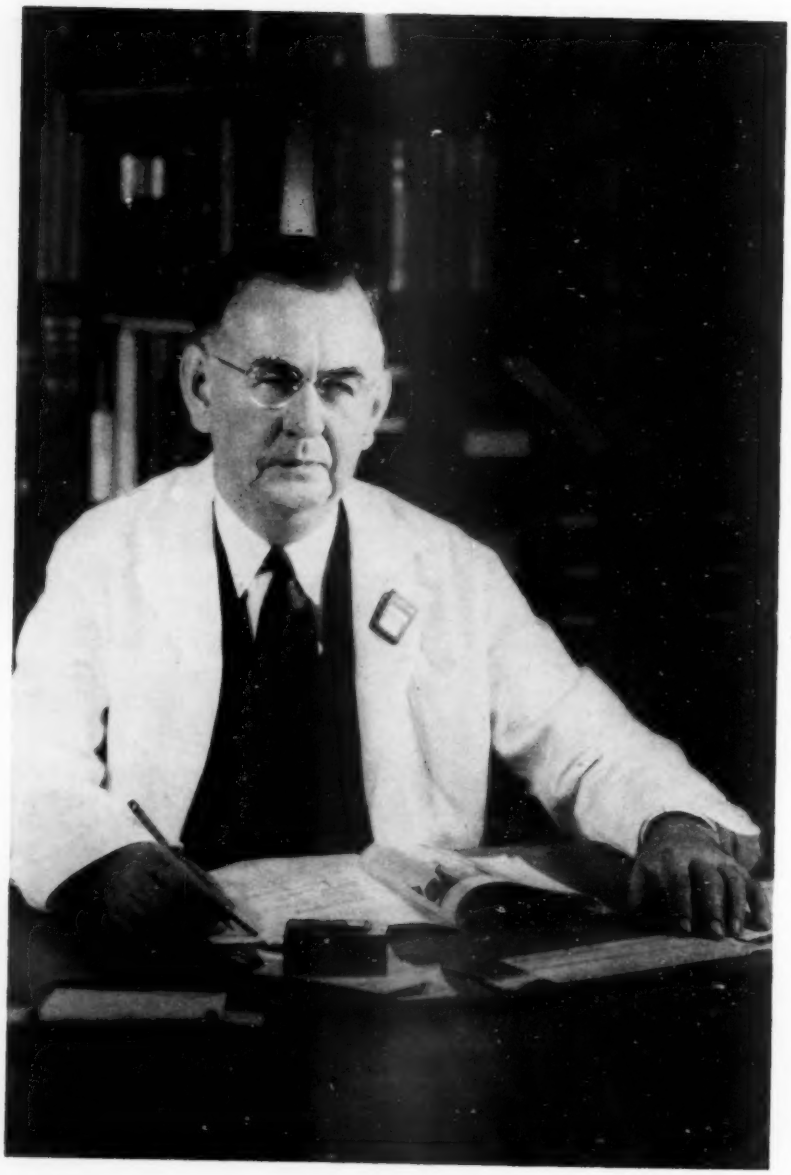
Thirteen patients with lymphosarcoma of the small intestine were observed at the Presbyterian Hospital, New York, from 1932 to 1947. Analysis of this series and a review of 179 patients reported in the literature from 1932–1948 showed that sometimes the disease was local in nature and was cured by complete excision. Three of the authors' patients and 23 reported in the literature survived five years or longer. There was a marked preponderance of males to females; the peak of distribution was in the fifth decade and the primary lesion was usually in the ileum.

Pain was present in all but two of the authors' patients. In almost every instance the symptoms which brought the patient to the hospital suggested chronic or acute ileus. Roentgenograms demonstrated dilated small bowel loops, but were not otherwise diagnostic.

There was no correlation between the duration of symptoms and the extent of the disease. The gross lesions were usually polypoid or infiltrative Annular constrictions were rare and complete obstruction was never present without intussusception. In the authors' series, the earliest lesions were confined to the mucosa rather than the submucosa. They also noted a lymphoid hyperplasia in the immediate vicinity of the tumor. In their series, 8 patients had metastases to the regional lymph nodes.

There was no constant correlation between clinical and pathological findings and prognosis. The presence of metastases in the lymph nodes did not preclude a cure. The type of lymphosarcoma had no influence on the prognosis except in the giant follicular type where it was more favorable. Only 2 cures of the disease in children could be found in the literature.

Postoperative irradiation seemed to improve but little the results of surgical treatment. Only 2 cures by irradiation alone were found in the literature.—*R. T. Levin, M.D.*



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